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Synthesis of Borylated Cyclobutanes via a Strain-Release 1,2-Metallate Rearrangement

Synthesis of Borylated Cyclobutanes via a Strain-Release 1,2-Metallate Rearrangement

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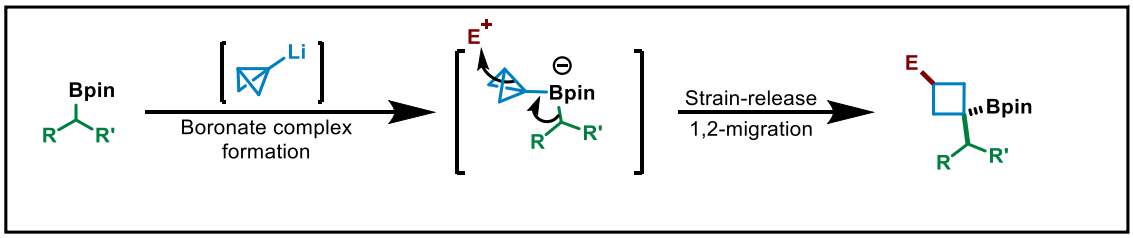
I. Abstract

Cyclobutanes are important motifs in natural products and are increasingly found in medicinal chemistry since they can provide a defined spatial arrangement of substituents. This thesis describes a new route to 1,1,3-trisubstituted cyclobutanes using a novel strain-release boronate complex. Specifically, reaction of lithiated bicyclo[1.1.0]butane with a boronic ester furnished an intermediate boronate complex which was reacted with a broad set of electrophiles. The electrophile and boronic ester substituent effectively add across the highly strained C–C σ-bond of the bicyclo[1.1.0]butane, which acts as a conjunctive reagent. This modular three-component coupling occurs with excellent levels of diastereoselectivity generating 1,1,3-trisubstituted cyclobutanes, decorated with an array of functional groups. The thesis also describes an improved route to lithiated bicyclo[1.1.0]butane.



II. Contents

III. Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ..... DATE:.....

IV. Acknowledgements

I would like to thank Varinder for the opportunity to work with him and his group. Your enthusiasm and drive have made this year an excellent learning experience.

Of course, I must thank Alex for guiding me over the past year. Your instruction has taught me a great deal about practising, writing and thinking about organic chemistry. It has been brilliant working with you to develop the project.

Adam, Beatrice and Alex Z, you have been very kind in taking time to discuss chemistry with me on several occasions. I am very grateful for these instructive discussions. ChangCheng, it has been a pleasure working alongside you. Thanks to members of N214 for a positive lab environment. The Aggarwal group, you have been very welcoming and have taught me so much about chemistry over the past year which has gone very quickly.

I must also thank Prof. J. Harrity (and lab), Dr B. Allen and Mr M. Wheatley whose encouragement led me to this lab. Harry, Hope and Liam for helping me settle in. I would also like to thank my friends and family, particularly Mum, Dad and my Grandparents.

V. Acronyms and Abbreviations

bicyclo[1.1.0]butane	bicyclobutane	DIDMH	*N,N'*-1,3-diiodb-5,5-dimethylhydantoin
Boc	*tert*-butyloxycarbonyl	e.e.	enantiomeric excess
Bpin	pinacol boronic ester	e.s.	enantiospecificity
m-CPBA	3-chloroperbenzoic acid	eq.	equivalents
cod	1,5-cyclooctadiene	MeTHF	2-methyl tetrahydrofuran
d.r.	diastereomeric ratio	NFSI	*N*-fluorobenzenesulfonimide
DB18C6	dibenzo-18-crown-6-ether	PTC	phase transfer catalysis
DBDMH	*N,N'*-1,3-dibromo-5,5-dimethylhydantoin	TBAS	tetrabutylammonium hydrogensulfate
DCDMH	*N,N'*-1,3-dichloro-5,5-dimethylhydantoin	TEBABr	benzyltriethylammonium bromide
DIAD	diisopropyl azodicarboxylate	TEBACl	benzyltriethylammonium chloride
DIBAL	diisobutylaluminium hydride	TFE	2,2,2-trifluoroethan-1-ol

1. General Introduction

1.1. General Strain-Release Chemistry

Strain theory was proposed by Adolf Von Baeyer in 1885, which hypothesised that three- and four-membered carbocycles would be less stable than five- and six-membered carbocycles as their C–C bond angles would deviate from ideality.[1] Since the theory's original proposal, it has been developed to account for bond lengths as well as torsional and angle strain.[2] The strain energy of a system is calculated as the difference between the observed enthalpy of formation and that expected for a hypothetical strain-free model, cyclohexane, with the same number and type of atoms.[3] Some examples of strained systems include: cyclopropane, which has a strain energy of 27.5 kcal/mol; cyclobutane, with a strain energy of 26.5 kcal/mol; and bicyclo[1.1.0]butane (referred to from this point on as bicyclobutane), which has a remarkably high strain energy of 63.9 kcal/mol (Figure 1), and for this reason has been described as "a unique chemical unit".[4]

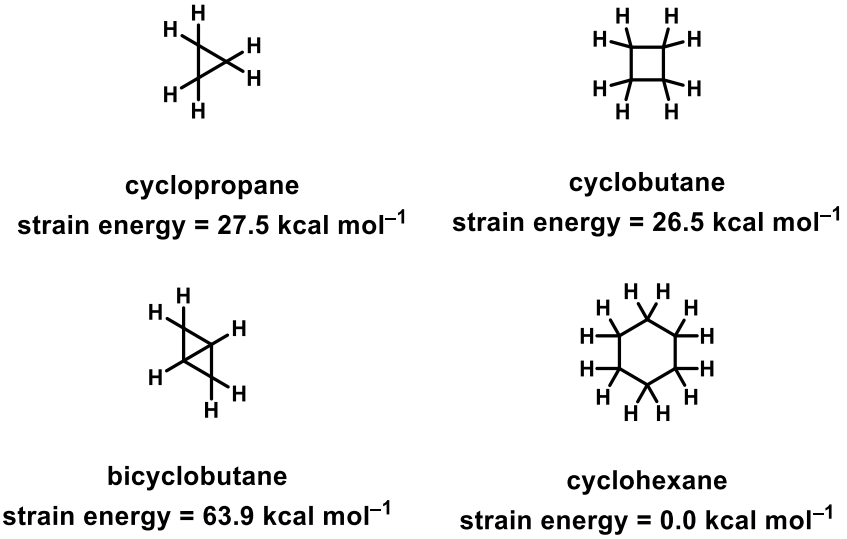


Figure 1: The strain energies of cyclopropane, cyclobutane and bicyclobutane.

Most bicyclic molecules possess a strain energy which is close to the sum of their constituent parts, but bicyclobutane has a strain energy greater than double that of cyclopropane, by 9 kcal/mol,[3] which results in some interesting physical and chemical properties. One such physical property is

the orbital character of the central bond, which has been shown both experimentally and with *ab initio* calculations to have high p-orbital character (Figure 2). While it may be expected that the 1,3-bond is elongated, because of poor orbital overlap and high p-orbital character compared to the other bonds in bicyclobutane, microwave spectroscopy has found that there is little difference between the 1,2- and 1,3-bond lengths, which are 1.498 Å and 1.497 Å, respectively.[5] A consequence of the high p-orbital character in the central bond is that the bridgehead C–H bonds have a higher s-character relative to an unstrained C(sp^3)–H bond, resulting in a stronger, but more acidic, C–H bond.[6]

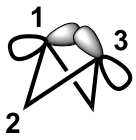
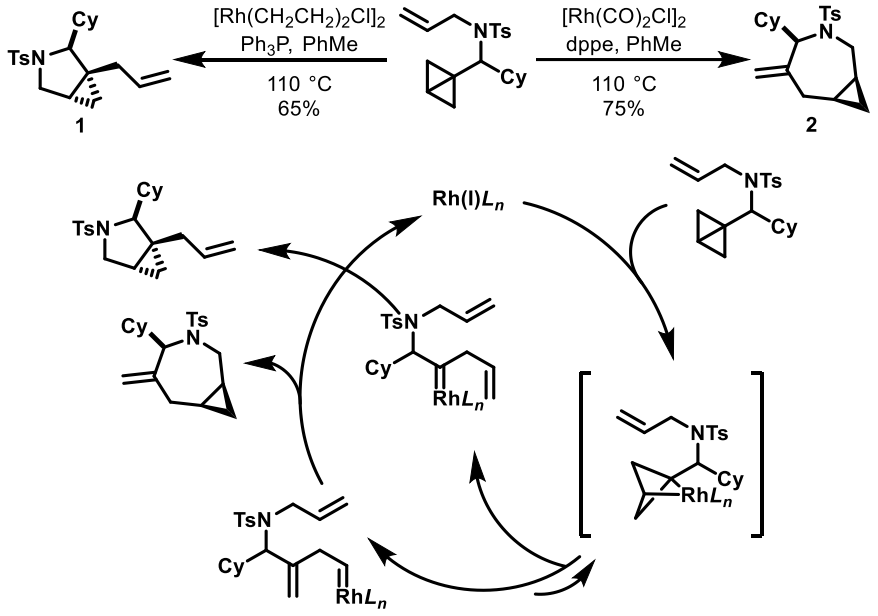


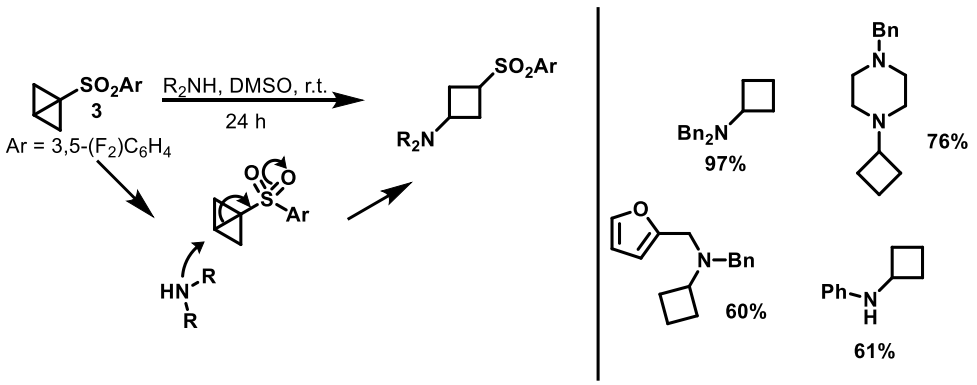
Figure 2: Bicyclobutane: orbital view of the central bond.

A variety of transformations are known for bicyclobutanes such as thermal ring opening, formal hydrogenation, acid-catalysed ring-opening, lithiation, diiodination and photocycloadditions.[6-7] Many of these reactions have used the strained 1,3-bond of bicyclobutane as a π-type bond. Recently, Wipf and co-workers developed a rhodium(I)-catalysed cycloisomerisation of substituted bicyclobutanes for the highly diastereo- and regioselective construction of heterocycles (Scheme 1).[8] While it is known that the bicyclobutane unit can undergo isomerisation under a variety of metal catalysed conditions,[9] its development was previously limited by low yield and a poor scope. Therefore, they developed conditions to selectively form one of two carbene intermediates which, after cyclopropanation of the *N*-allyl group, afforded either pyrrolidine **1** or azepine **2** with good levels of control and yield. The carbene formation is proposed to be dictated by the steric bulk of the phosphine ligands used, although it may be reversible.



Scheme 1: Bicyclobutyl isomerisation to form nitrogen-containing heterocycles.

Baran and co-workers have used bicyclobutyl sulfones to perform strain-release amination reactions. Here, the strained 1,3-bond of bicyclobutyl sulfone **3** acted as an electrophile for nucleophilic amines to attack (Scheme 2).[10-11] This was successful for a range of primary and secondary amines, occurring in moderate to excellent yields. The chemistry was extended to bioconjugation, where cysteine thiols were used as nucleophiles to directly append the cyclobutyl ring to peptides. These reactions exemplify bicyclobutanes as "privileged tools for discovering new reactions".[12]



Scheme 2: Strain-release amination of bicyclobutyl sulfones.

1.2. Cyclobutanes

1.2.1. General Introduction to Cyclobutanes

Cyclobutanes are four-membered carbocycles which have attracted attention due to their value as chemical intermediates,[13] as well as a result of their presence in nature and their related biological activities.[14] Figure 3 shows a range of natural and biologically active products which contain the cyclobutane moiety, such as the pleasant smelling pinene, caryophyllene,[15] which has anticancer activity affecting growth and proliferation in many cancer cell lines,[16] and cyclobut-A, which has potent activity against HIV *in vitro*.[17]

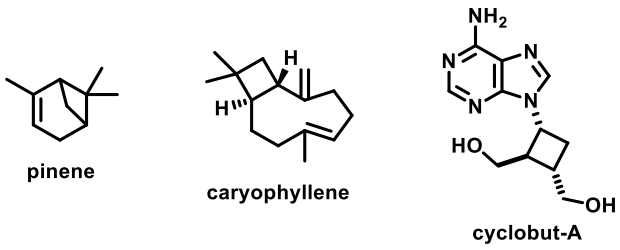


Figure 3: Natural or bioactive molecules containing cyclobutanes.

In addition to being valuable targets, they can be useful synthetic intermediates as they possess a strain energy of 26.5 kcal/mol because of reduced bond angles (88 °), relative to unstrained C(sp^3)–C(sp^3) bonds (109.5°), and a transannular interaction, which is caused by puckering (Figure 4). Applications of cyclobutane derivatives, predominantly cyclobutanones, in catalysis highlight some of the transformations they can undergo, such as C–C bond activation.[18-19]

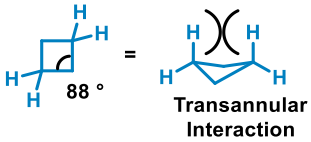
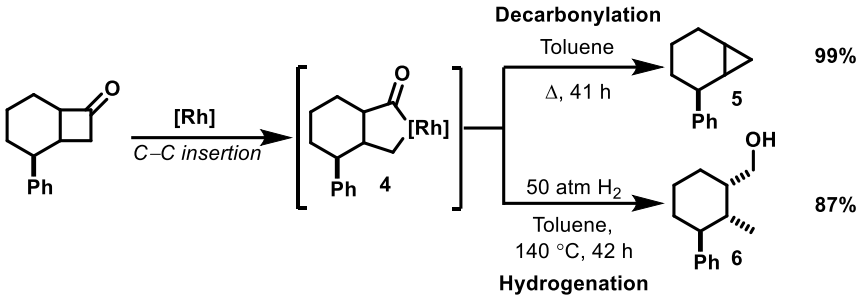


Figure 4: Conformation of cyclobutanes.

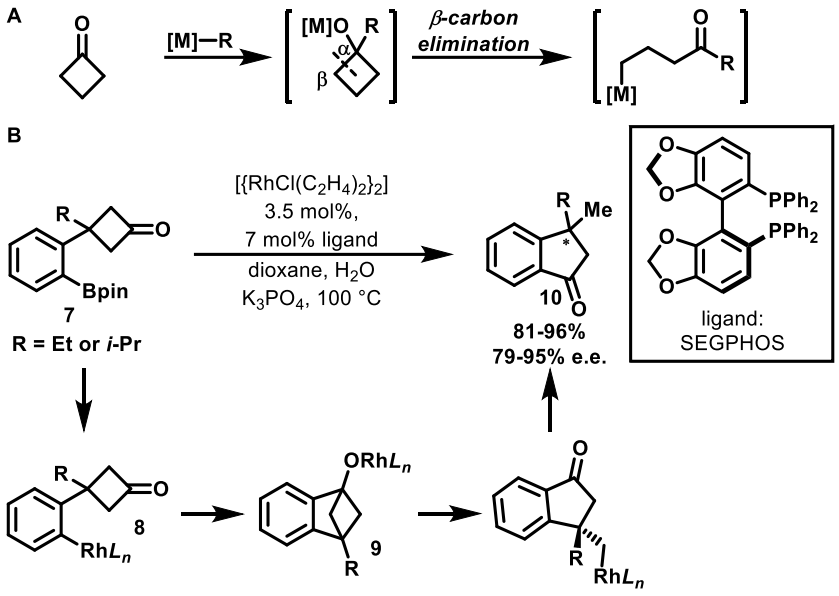
First described by Ito and co-workers in 1994, a rhodium(I) catalyst underwent an oxidative insertion into a carbonyl–carbon bond of a cyclobutanone to form rhodacycle **4** (Scheme 3).[20] This

intermediate can then be used to produce a range of products including cyclopropanes **5**, via decarbonylation, or alcohols **6**, after hydrogenation.



Scheme 3: Rhodium(I) insertion into cyclobutanone for cyclopropane formation and hydrogenation via an intermediate rhodacycle.

The intramolecular process of breaking a C–C bond, where a metal is bonded to a C, N or O, can occur through β-carbon elimination. For strained systems such as cyclobutanes, this relieves the ring strain and forms a reactive organometallic intermediate which can participate in further reactions (Scheme 4A).[21-22] Murakami and co-workers exploited the β-carbon elimination of cyclobutanones to form products containing chiral benzylic quaternary centres with high levels of enantioselectivity (Scheme 4B).[23] They propose a mechanism which proceeds by transmetallation of the boronic ester **7** with the rhodium catalyst. The rhodium species **8** then intramolecularly inserts into the carbonyl–carbon bond to form a bicyclo[2.1.1]hexane **9** which undergoes β-carbon elimination and protonolysis to give the products **10** in good to excellent yields and enantioselectivities.



Scheme 4: A) Generalised β-carbon elimination of a cyclobutanone. B) Chiral benzylic quaternary carbon formation via β-carbon elimination.

1.2.2. Synthesis of Cyclobutanes

There are many methods for making cyclobutanes, some are shown (Figure 5), which include ring contraction and expansion, cyclisation and [2+2] photocycloaddition reactions.

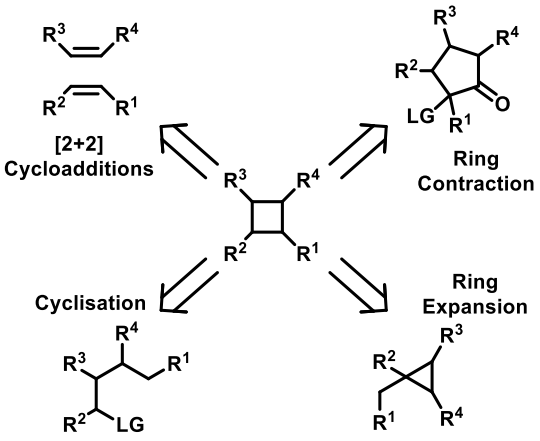
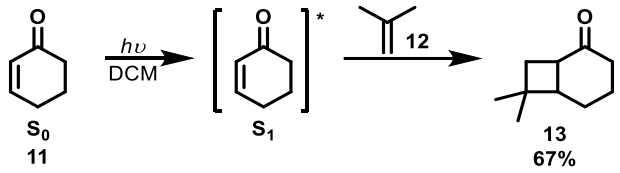


Figure 5: Possible retrosyntheses of cyclobutanes.

The [2+2] photocycloaddition reaction is one which occurs between two different alkenes, for example, an enone and a simple unsaturated alkene. The reaction proceeds when one alkene, such as cyclohexenone **11**, absorbs UV light, which results in the alkene being excited from the ground state (S_0) to an excited state (S_1).[24] This excited alkene can then add to isobutene **12** (which has not been excited due to the excited state being significantly higher in energy) by a [2+2]

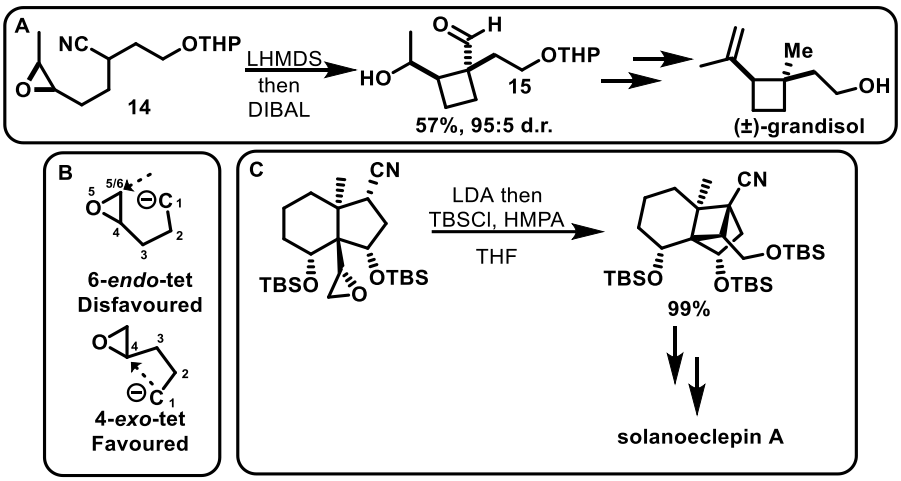
photocycloaddition, to give the product **13** (Scheme 5).[25] The [2+2] photocycloaddition reaction has been utilised as a key step in several total syntheses which is an important challenge of a methodology as it is applied in a complex setting.[26] An attractive feature of these reactions is their ability to form multiple C–C bonds in a single transformation, allowing one to take simple precursors and quickly build up molecular complexity. As a result of its widespread application, the reaction has been developed in several areas including the use of visible light, application in flow chemistry, enantioselective catalysis and photoinduced electron transfer.[25] However, the methodology has limitations such as high lying S_1 for many alkenes, which requires high energy light and limits functional group tolerance as the reaction can become non-specific. Moreover, these sources of light are not readily available. Other limitations include regioselectivity issues with respect to head-to-head and head-to-tail coupling, as well as *E*/*Z* isomerisation which can occur under commonly employed reaction conditions.



Scheme 5: A [2+2] photocycloaddition of cyclohexenone and isobutene via an excited alkene.

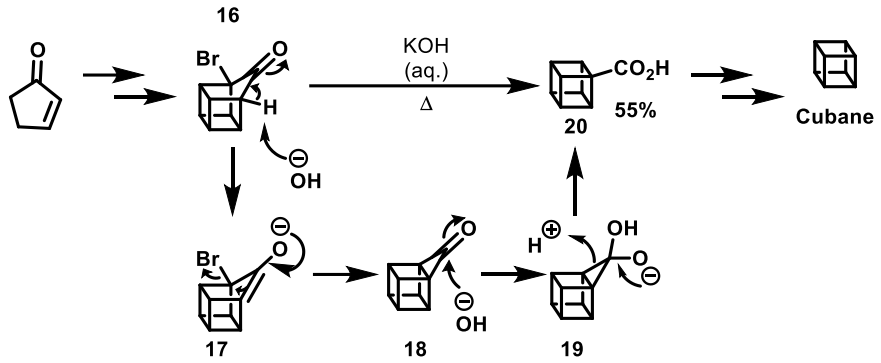
Other syntheses of cyclobutanes have also been developed. For example, Stork and co-workers found that an intramolecular epoxynitrile cyclisation could form the cyclobutane core en route to the synthesis of (±)-grandisol (Scheme 6A).[27] Here, deprotonation with lithium bis(trimethylsilyl)amide (LHMDS) at the α-position of the nitrile **14** resulted in a formal carbanion, which can cyclise to afford the cyclobutane **15**, after reduction with diisobutylaluminium hydride (DIBAL), with excellent levels of diastereoselectivity. The cyclisation can be rationalised as it is a 4-*exo*-tet process, which is favoured by Baldwin's rules (Scheme 6B). The formation of a five-membered ring could be described as a 5-*exo*-tet cyclisation which is favourable by Baldwin's rules. However, the *cis*-substituted epoxide obstructs this pathway and the cyclisation occurs with a six-

membered transition state where the nucleophile, electrophilic carbon and leaving group must align at 180 ° for attack to occur, which is kinetically unfavourable. Furthermore, the transition state has a disfavoured 6-*endo*-tet character, which would be an equally valid description of the cyclisation.[28] This strategy has been deployed in a synthesis of solanoeclepin A by Miyashita and co-workers in 2011, showing its ability to be used in other complex settings (Scheme 6C).[29]



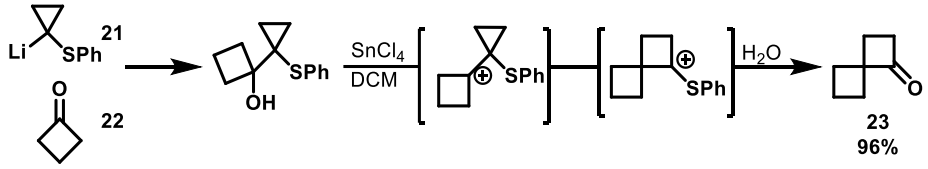
Scheme 6: A) Intramolecular cyclisation of an epoxynitrile to form a cyclobutane en route to the synthesis of (±)-grandisol. B) Rational for the cyclisation to form a 4-membered ring. C) The application of the cyclisation in the synthesis of solanoeclepin A.

Ring contractions have also been used for cyclobutane synthesis. The highly strained cubane was synthesised, first by Eaton, using a Favorskii rearrangement (Scheme 7).[30] This involves the deprotonation of a cyclic α-bromoketone **16** to form an enolate **17**, which cyclises with displacement of bromide to form a fused cyclopropanone **18**. A nucleophile can then attack the carbonyl, to give a tetrahedral intermediate **19** which subsequently collapses to form, after protonation, the ring contracted product **20**.[31]



Scheme 7: Eaton's synthesis of cubane using a Favorskii ring contraction to form a cyclobutane ring.

The reverse strategy, ring expansion, is an alternative way of forming cyclobutanes. Trost and co-workers developed a method for making cyclobutanes via a ring expansion which relied on the formation of lithiated cyclopropyl phenyl sulfides such as **21**.[32] Treatment of this lithiated species with ketone **22** and stannic chloride gave, after hydrolysis, cyclobutanone **23** (Scheme 8).



Scheme 8: Ring expansion of cyclopropanes to form cyclobutanones.

1.3. Organoboron Chemistry

Organoboron compounds are indispensable in modern synthesis due to their utility in cross-coupling and extensive use in asymmetric synthesis.[33-34] Neutral boron atoms form three bonds, with 6 valence electrons, so the boron atom is sp^2-hybridised. This hybridisation causes the substituents to adopt a trigonal planar geometry, where the empty p-orbital is orthogonal to the substituents (Figure 6A). When the boron atom is bonded to two oxygen atoms and one carbon atom, it forms a particularly useful class of organoboron compounds known as boronic esters, such as cyclohexyl pinacol boronic ester **24** (Figure 6B).[35] These are air-stable and require no special techniques for handling, making their manipulation easy to perform. Here, the lone pairs on the oxygen atoms donate electron density into the empty p-orbital of the boron atom, which stabilises

boronic esters relative to boranes (Figure 6C). However, the vacant p-orbital of the boron atom, in boronic esters, can still be attacked by a suitable nucleophile to form boronate complexes.

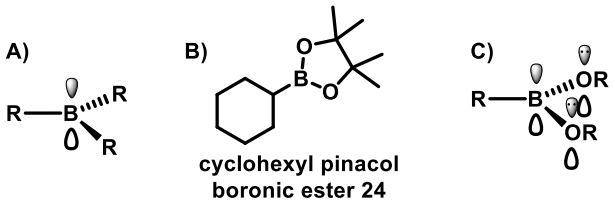


Figure 6: A) The empty p-orbital of the boron atom. B) Cyclohexyl pinacol boronic ester. C) Electron donation from oxygen lone pairs into the empty p-orbital on boron.

These properties of boronic esters make them one of the most versatile functional groups in organic synthesis, which can undergo several stereoselective transformations such as oxidation,[36] amination[37] and homologation[38-39] (Figure 7).

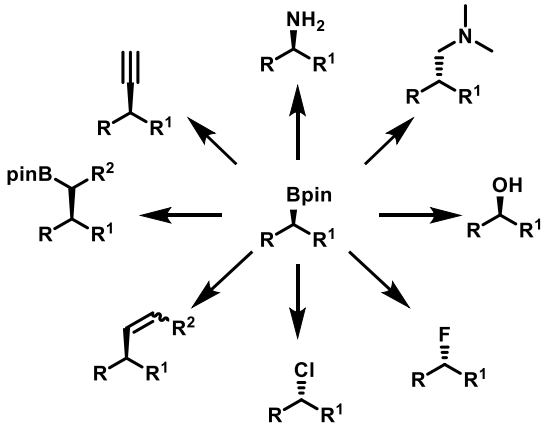
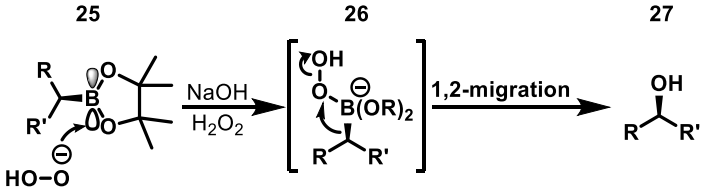


Figure 7: A selection of secondary boronic ester transformations and functionalisations.

1.3.1. Boronate Complexes with an α-Leaving Group

When a nucleophile attacks the empty p-orbital of a boron atom, a tetrahedral complex is generated with an overall negative charge known as a boronate species. An electron deficient carbon α to a boronate complex can trigger a 1,2-migration of a boron substituent. This process is termed a 1,2-metallate rearrangement and this is highlighted by the stereospecific oxidation of an organoboron to the corresponding alcohol.[40] Scheme 9 shows the mechanism whereby a nucleophilic peroxide anion attacks the empty p-orbital of a secondary enantiopure boronic ester **25** to form a tetrahedral boronate complex **26**.[41] Subsequent 1,2-metallate rearrangement with concerted expulsion of the

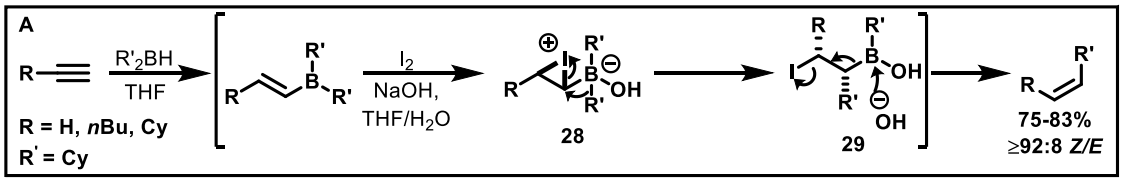
leaving group (a hydroxide anion) occurs in an antiperiplanar conformation with respect to the leaving group and migrating group (the carbon atom). After the hydroxide has attacked the boron atom to break the O–B bond, the corresponding alcohol **27** is afforded with retention of configuration at the migratory carbon.[31]



Scheme 9: Formation of a boronate complex and a 1,2-metallate rearrangement as exemplified by oxidation of an enantiopure secondary boronic ester to the corresponding alcohol.

1.3.2. Vinyl Boronate Complexes in Zweifel Coupling

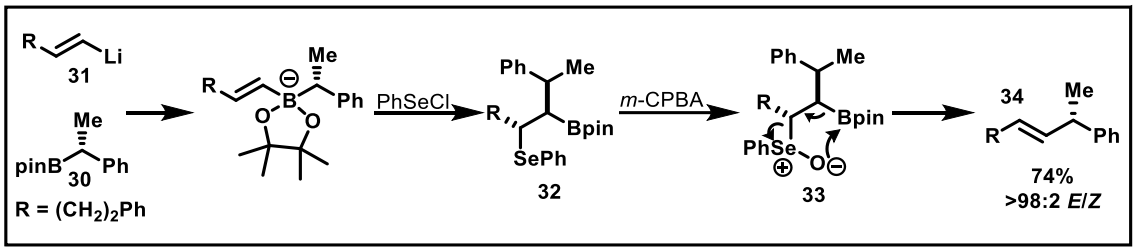
In 1967, Zweifel and co-workers studied the hydroboration of alkynes to give borylated alkenes, which were subsequently treated with iodine to give an iodonium intermediate **28** (Scheme 10).[42] After boronate formation using sodium hydroxide, a 1,2-metallate rearrangement occurred to produce β-iodoboron species **29**. When another hydroxide ion attacks the borinic ester, it causes *anti* elimination of the boron species and iodine to afford *Z*–alkenes. Initially, this coupling was limited to boranes, but has since been developed to include borinic and boronic esters.[43]



Scheme 10: Zweifel coupling.

A stereodivergent method has been developed by Aggarwal and co-workers where electrophilic iodination or selenation of a alkenyl boronate complex can result in a stereospecific *anti* or *syn* elimination to access either *E*– or *Z*–alkenes (Scheme 11).[44] For example, boronic ester **30** reacts with vinyl lithium **31** (formed via lithium-halogen exchange of the corresponding vinyl halide) to

form a boronate complex, which then undergoes electrophilic selenation and 1,2-metallate rearrangement to give **32**. Chemoselective oxidation of the selenium with *meta*-chloroperbenzoic acid (*m*-CPBA) gives the β-selenoxyboronic ester **33**, which can participate in *syn* elimination of the selenoxy species and the boronic ester to produce *E*-alkene **34** with excellent selectivity and 100% enantiospecificity (e.s.) (enantiospecificity defined as: (enantiomeric excess (e.e.) of the product/e.e. of starting material) ×100).[45]

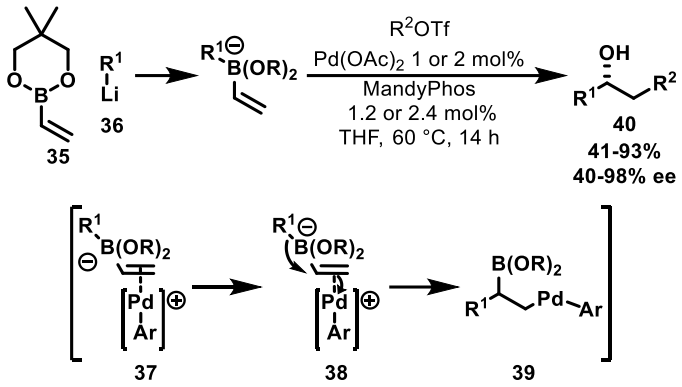


Scheme 11: Zweifel coupling using selenium for a stereodivergent approach.

1.3.3. Vinyl Boronate Complexes in Multicomponent Coupling

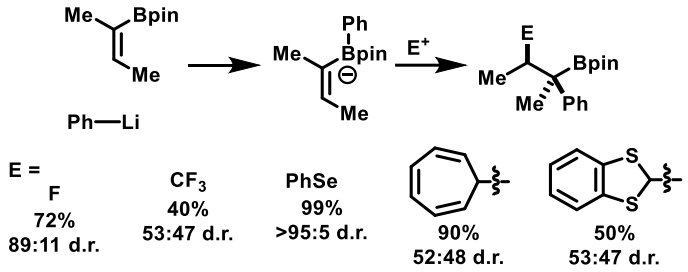
Recently, several three component coupling reactions have showcased the power of performing a cross-coupling reaction across a conjunctive reagent to rapidly increase molecular complexity in a single transformation.[46] Commonly, C–C π-bonds are used, as they can act as both an electrophilic and nucleophilic component. Morken and co-workers described a conjunctive cross-coupling, where two nucleophilic species are combined to one, in the enantioselective 1,2-functionalisation of vinyl boronic esters with organolithiums (or boronic esters and vinyl lithiums) and an aryl or vinyl triflate (Scheme 12).[47] Mechanistically, this occurs by the boronic ester **35** trapping the organolithium **36** to form a vinyl boronate complex, where the π-system can co-ordinate to an electrophilic palladium-aryl complex **37** to induce a 1,2-metallate rearrangement **38**. The resulting palladium complex **39** can then undergo reductive elimination to continue the catalytic cycle and afford the conjunctive cross-coupled product **40**. The overall transformation forms two new C–C bonds with a vicinal relationship and retains the boronic ester, although it was oxidised in this case to aid isolation. The reaction was shown to be successful using a range of alkyl and aromatic

organolithiums. Both aryl and vinyl triflates were originally reported with the following functionalities present: ester, acetal, aldehyde and an ether. Further investigation showed that aryl halides and Grignards, which initially inhibited catalytic turnover due to halide anions outcompeting the vinyl boronate complex for binding to palladium, could be used when sodium triflate was present. This acts to activate the Grignard, for full boronate complex formation, and as a halide scavenger.[48]



Scheme 12: Morken's conjunctive cross-coupling of an organolithium, boronic ester and aryl or vinyl triflate.

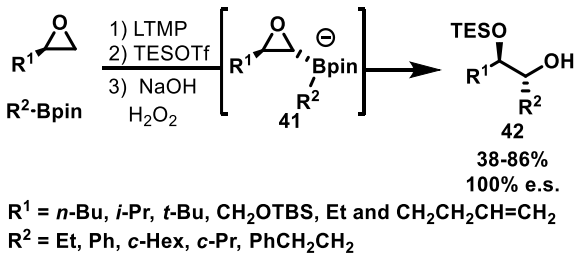
Aggarwal and co-workers conceived an interrupted Zweifel as a means of developing a three-component coupling without the need for a transition metal catalyst.[49] Previous work (section 1.3.3.) showed that vinyl boronate complexes could react with phenyl selenium chloride to form a β-selenoboronic ester **32**. To establish a broader scope, a range of secondary boronic esters were shown to react with good yield and with excellent diastereoselectivity. Other electrophilic reagents were also successful, allowing the incorporation of cycloheptatriene, fluorine, a trifluoromethyl group and benzodithiole (Scheme 13). Diastereoselectivity varied for each electrophile, with high diastereoselectivity being observed in cases where electrophiles formed a closed three-membered ring, activating the boronate complex, for example phenyl selenium chloride. Electrophiles which do not form closed three-membered intermediates, such as tropylium tetrafluoroborate, result in almost no diastereoselectivity.



Scheme 13: Conjunctive functionalisation of boronate complexes with electrophiles.

1.3.4. Strain-Release Boronate Chemistry

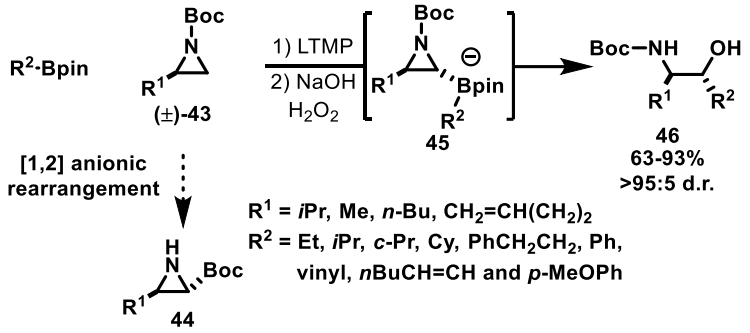
In 2009, Aggarwal and co-workers reported that lithiation (using lithium tetramethylpiperidine (LTMP)) of epoxides in the presence of a boronic ester formed a boronate complex **41** which, after 1,2-metallate rearrangement, breaks the strained C–O bond of the epoxide.[50] The generated alkoxide was then protected using triethylsilyl trifluoromethane sulfonate (TESOTf) and the boronic ester oxidised to the corresponding alcohol which gave a variety of 1,2-diols **42** in moderate to good yield and with 100% e.s. (Scheme 14). The work shows that the release of strain energy can be used as a driving force for the 1,2-metallate rearrangement of boronate complexes.



Scheme 14: Epoxides in a strain-release 1,2-metallate rearrangement of a boronate complex.

Aggarwal and co-workers successfully extended a similar chemistry to protected aziridines **43** to produce β-amino alcohols (after oxidation of the boronic ester).[51] Lithiation of the aziridine is *trans*-specific for *N*–*tert*-butyloxycarbonyl (Boc) (shown) and *N*–*tert*-butylsulfonyl (not shown) protected aziridines (Scheme 15). However, the boronic ester must be present during lithiation, and therefore compatible with the base, otherwise, an intramolecular [1,2] anionic rearrangement can occur to give the aziridyl ester **44**. They found that LTMP successfully lithiates the aziridine which can then be trapped by the boronic ester to form a boronate complex **45**. The reaction then proceeds

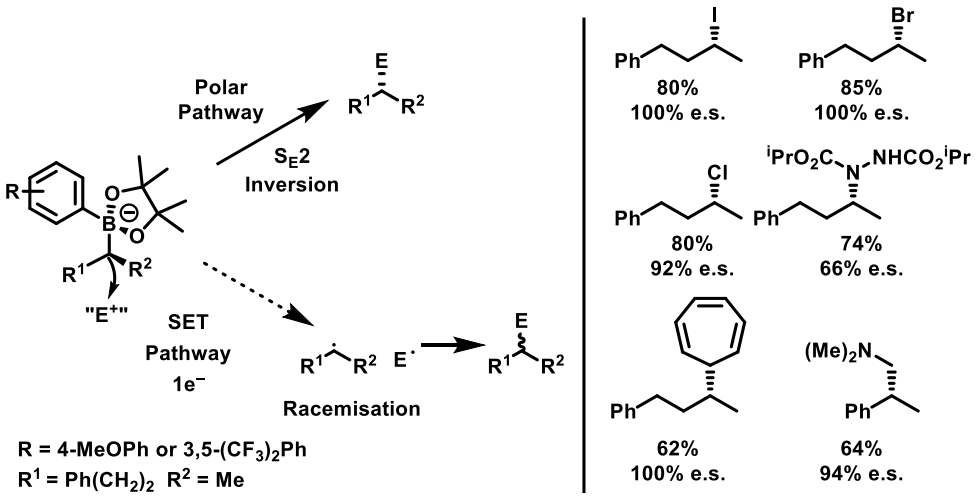
in an analogous manner to that described for lithiated epoxides to give a range of substituted β-amino alcohols **46** in moderate to excellent yield with excellent diastereoselectivity.



Scheme 15: Protected aziridines in a strain-release 1,2-metallate rearrangement of a boronate complex.

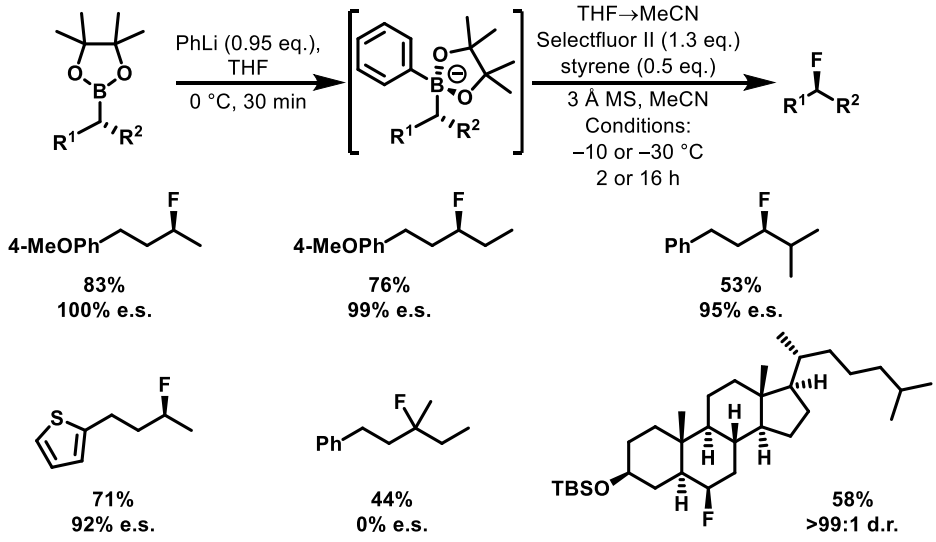
1.3.5. Nucleophilic Boronate Complexes as Chiral Nucleophiles

A boronate complex can only undergo a 1,2-metallate rearrangement when there is a group on the migratory terminus which can either be expelled, such as a leaving group or a strained bond which can be broken (section 1.3.1.and 1.3.4.), or when the terminus is unsaturated and so can react with an electrophile (section 1.3.2. and 1.3.3.). When the terminus is saturated with no leaving group or strained bond, a primary or secondary boronic ester will react with an aryl lithium to form a chemically and configurationally stable boronate complex. Aggarwal and co-workers established that enantioenriched secondary boronate complexes could directly act as a nucleophile via an electrophilic substitution (S_E2) pathway of the C–B bond, causing inversion of stereochemistry at the nucleophilic carbon. This has been shown for a range of boronic esters and electrophiles (Scheme 16).[52] While the reaction proceeds with high e.s., in many cases, it is often not perfect due to a competing single electron transfer (SET) pathway.



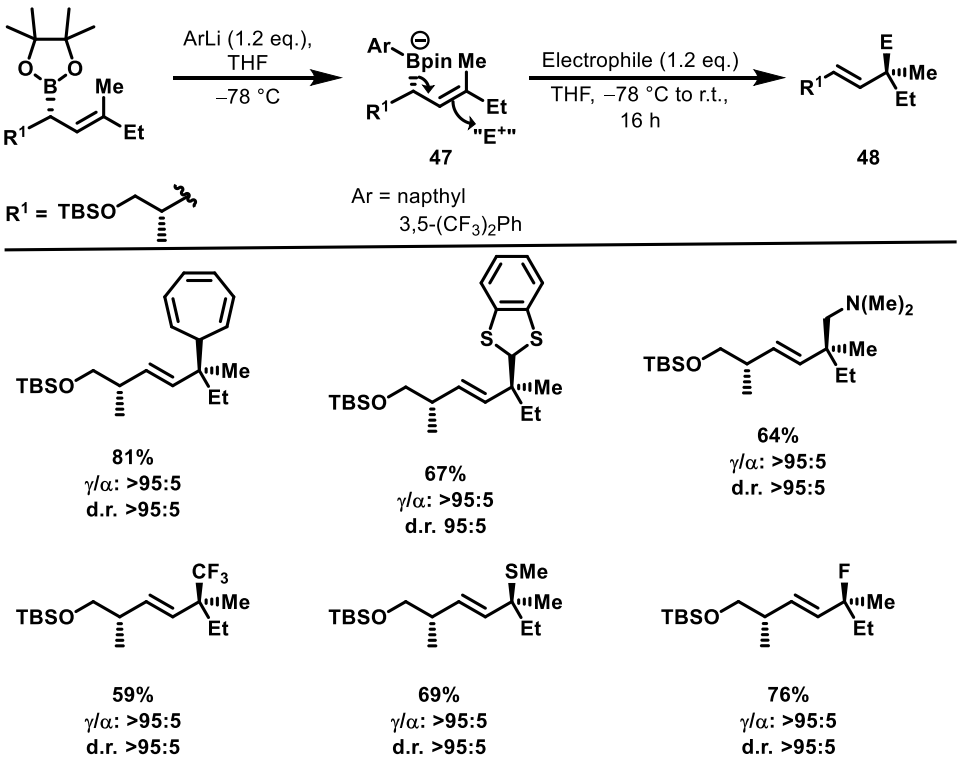
Scheme 16: Reaction of nucleophilic boronate complexes with a range of electrophiles.

This chemistry was later investigated to achieve the synthesis of enantioenriched secondary alkylfluorides.[53] The competing SET mechanism was found to be suppressed by the addition of styrene, which acted as a radical scavenger to inhibit a radical propagation cycle.[34] The reaction allowed a variety of secondary alkylfluorides to be accessed in moderate to excellent yield with high levels of e.s. (Scheme 17). Despite the success with secondary boronic esters, a tertiary example showed no enantiospecificity. The mechanism is proposed to be identical to the nucleophilic boronate complex chemistry described.



Scheme 17: Synthesis of enantioenriched alkylfluorides from secondary boronic esters via nucleophilic boronate complexes.

A recent development has found that enantioenriched allyl boronate complexes can also react with a range of electrophiles through the allylic C–C π-bond, affording quaternary stereogenic centres with high stereocontrol.[54] Mechanistically, this occurs by the boronate complex **47** being eliminated with trapping of the electrophile at the γ-position to produce **48** in an S_E2' fashion (Scheme 18). This was initially investigated using tropylium tetrafluoroborate as an electrophile, which found that naphthyl and 3,5-$(CF_3)_2$phenyl lithium gave high yields with excellent γ/α selectivity and high diastereoselectivity. These conditions were then used to expand the electrophile scope to give products containing tertiary (not shown) or quaternary stereogenic centres.

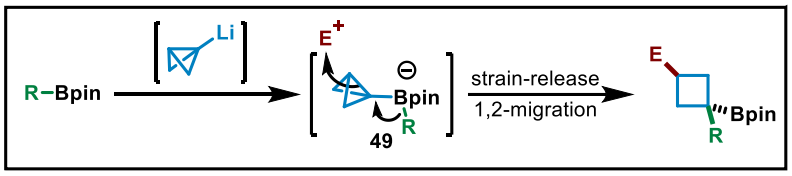


Scheme 18: Reaction of allyl boronate complexes with a variety of electrophiles.

2. Optimising the Synthesis of 1,1-Dibromo-2-(chloromethyl) Cyclopropane

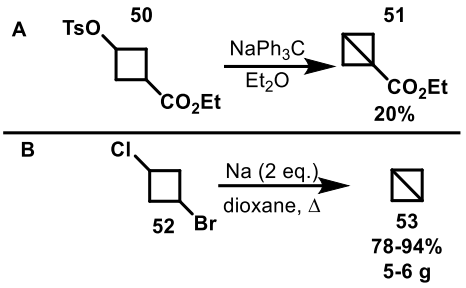
2.1. Introduction

The Aggarwal group was interested in cleaving a C–C σ-bond using a 1,2-metallate rearrangement, which would represent a new reactivity mode of boronate complexes.[55] As C–C σ-bonds do not readily cleave and have not previously been observed to break in a 1,2-metallate rearrangement of a boronate complex, it was envisaged that a highly strained system would be required if a C–C σ-bond were to be broken. As bicyclobutane is known to have a particularly high strain energy, this was considered as a promising strained reagent. Breaking the strained bond, after a 1,2-metallate rearrangement, would result in the creation of a carbon σ-bond nucleophile **49**, which could react with an electrophile (Scheme 19). Thus, a strained C(sp^3)–C(sp^3) σ-bond would act as a conjunctive reagent, rather than an unsaturated system like those previously described (sections 1.3.2 and 1.3.3.).



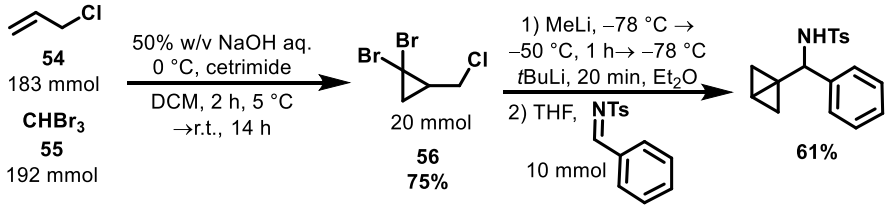
Scheme 19: The concept of a strain-release 1,2-metallate rearrangement using a bicyclobutyl boronate complex.

There are several literature procedures for forming the bicyclobutyl unit, which was first synthesised by Wiberg in 1959 by treating ethyl 3-(tosyloxy)cyclobutane-1-carboxylate **50** with sodium triphenylmethide to give bicyclobutyl ester **51** (Scheme 20A).[2, 56] Later, Lampman produced multiple grams of bicyclobutane **53** using a Wurtz reaction, where sodium metal, enables an intramolecular cyclisation of 1-bromo-3-chlorocyclobutane 5**2** (Scheme 20B).[57] Despite the high yield, the reaction is limited as it requires the use of specialised glassware, which is not easily obtained, and use of sodium metal, which makes the reaction hazardous. Moreover, impurities contaminate the bicyclobutane obtained, which is a gas at ambient temperature and not trivially purified or handled.



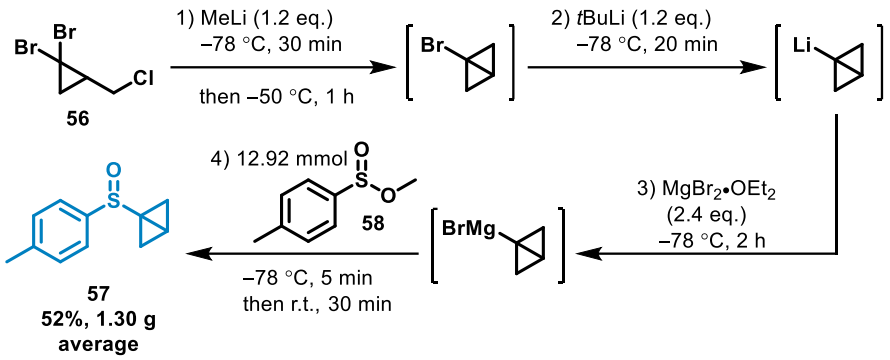
Scheme 20: A) The first synthesis of bicyclobutane as an ester derivative. B) Gram-scale synthesis of bicyclobutane.

Wipf and co-workers synthesised substituted bicyclobutanes by trapping a lithiated bicyclobutane with several different imines (Scheme 21) (section 1.1.).[8] The bicyclobutanes were synthesised from cyclopropane **56**, which was synthesised according to a procedure developed by Neuenschwander for the cyclopropanation of allyl chloride **54** with bromoform **55**.[58]



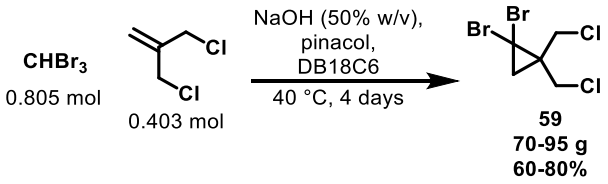
Scheme 21: Formation of substituted bicyclobutanes.

This synthesis of lithiated bicyclobutane[8] is cumbersome to perform as the two steps require varying the temperature between –78 °C and –50 °C. Further, the complication of forming the lithiated bicyclobutane from the cyclopropane could result in several species affecting the reaction outcome. To address these issues, a convenient precursor was conceived that would enable the synthesis of lithiated bicyclobutane in a quick and simple step. Aggarwal and co-workers invented bicyclobutyl sulfoxide **57** as a reagent which fulfilled these criteria, which is an easy-to-handle crystalline reagent which can undergo lithium-sulfoxide exchange[59] to form lithiated bicyclobutane in 5 minutes. They found that the bicyclobutyl sulfoxide **57** can be made via transmetalation of the lithiated bicyclobutane to the Grignard bicyclobutane which is then trapped with sulfinate ester **58** (Scheme 22). This reaction can be reproducibly performed on gram-scale.



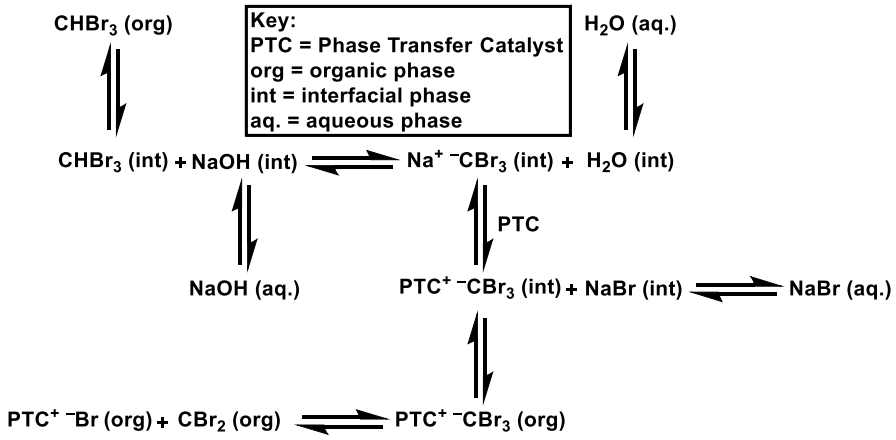
Scheme 22: Synthesis of bicyclobutyl sulfoxide.

The availability of cyclopropane **56**, necessary to access bicyclobutyl sulfoxide **57**, was limited as attempts by Aggarwal and co-workers[60] to reproduce the results observed by Neuenschwander[58] and Wipf,[8] resulted in yields of 20-27%, and not 75%. To improve this, an optimisation study was carried out, based on conditions developed by Daily on a related system (Scheme 23).[61] Under these conditions, dibenzo-18-crown-6 ether (DB18C6) was used as a phase transfer catalyst, with pinacol acting as a co-catalyst, and an aqueous sodium hydroxide solution as the base. The cyclopropanation reaction afforded the *gem*-dibromocyclopropane **59**, which was used as a precursor towards [1.1.1]propellane.



Scheme 23: Synthesis of a [1.1.1]propellane precursor.

The mechanism of forming *gem*-dibromocyclopropanes using phase transfer catalysis is proposed to involve several steps starting with deprotonation of bromoform in the interfacial region of the biphasic mixture (Scheme 24).[62] The tribromomethyl anion produced, with a sodium counterion can then be complexed to a catalyst, for example crown ethers, or undergo ion exchange with a catalyst like a tetraalkylammonium salt to form a lipophilic ion pair. The ion pair can then enter the organic phase where reversible dissociation occurs to give the carbene which can react with the alkene to form a *gem*-dibromocyclopropane.



Scheme 24: The mechanism of carbene formation under phase transfer catalysis conditions.

2.2. Project Aim

We initially wished to optimise the synthesis of 1,1-dibromo-2-(chloromethyl)cyclopropane **56** from bromoform and allyl chloride.

2.3. Results and Discussion

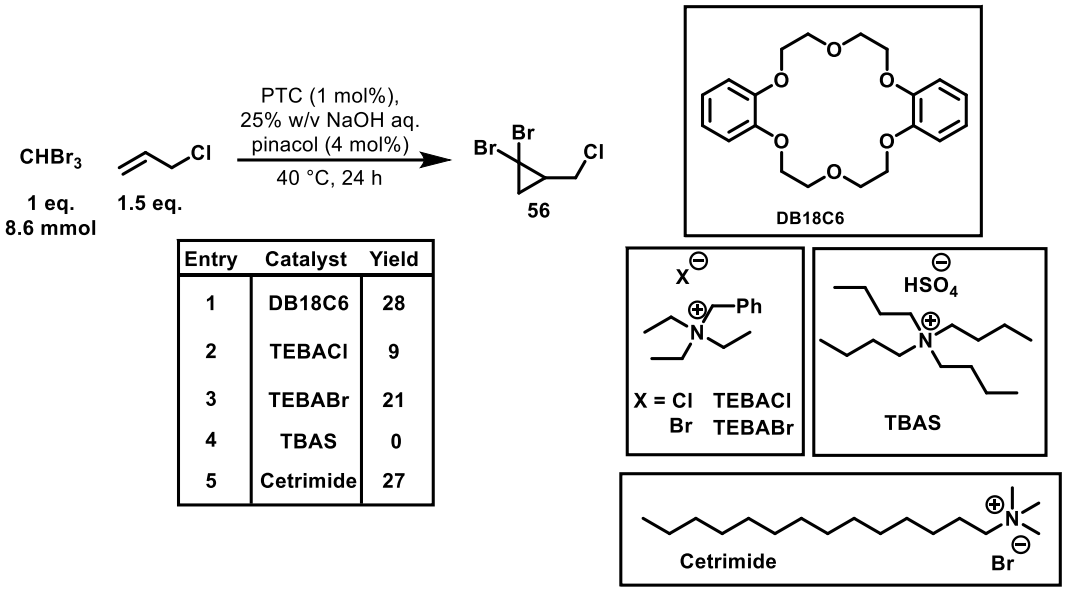
2.3.1. Phase Transfer Catalysed Cyclopropanation of Allyl Chloride with Bromoform

The conditions for the synthesis of **59** were used with allyl chloride, but running the reaction over 24 h with an aqueous sodium hydroxide solution concentration of 25% w/v, bromoform was the limiting reagent as it was found that purifying the product by flash column chromatography was complicated if unconsumed bromoform remained.[I] These conditions gave cyclopropane **56** in 28% isolated yield[II] (Scheme 25, entry 1). A review by Fedoryński highlights a variety of conditions which can be used for *gem*-dihalocyclopropanation of alkenes under phase transfer catalyst conditions.[62] Other popular catalysts include tetraalkylammonium salts, such as triethylbenzylammonium chloride (TEBACl) which resulted in a 9% yield (entry 2) and the bromide analogue (TEBABr) gave 21% yield, suggesting the counter ion has a non-innocent role

[I] This was found by A. Fawcett and is included in this thesis to provide a complete picture of the work.

[II] We found the product to be slightly volatile under vacuum and so it was isolated alongside residual pentane. The yields were corrected for this.

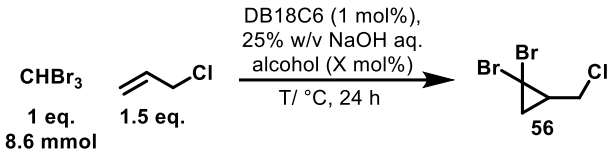
(entry 3). Other quaternary ammonium salts, tetrabutylammonium sulfonate (TBAS) and cetrimide, were both used and found to give no isolated product and 27% yield, respectively (entries 4 and 5).



Entry	Catalyst	Yield
1	DB18C6	28
2	TEBACl	9
3	TEBABr	21
4	TBAS	0
5	Cetrimide	27

*Scheme 25: Catalysts screen in the phase transfer catalysed synthesis of cyclopropane **54** and catalyst structures.*

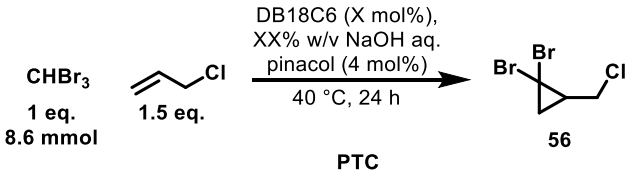
With DB18C6 proving to be the most effective catalyst, we next explored the reaction temperature (Scheme 26, entry 1, 2 and 3). At ambient temperature, 60 and 80 °C, the reaction resulted in reduced yields of 17, 9 and 6%, respectively. The lower yield at a higher temperature could be due to the volatility of allyl chloride, which has a boiling point of 44–46 °C, so loss of allyl chloride could occur if the system was not effectively sealed. As there were no improved yields after briefly investigating temperature, other variables were studied. The role of pinacol in phase transfer catalyst reactions has been suggested to be co-catalytic with the phase transfer catalysed deprotonation, accelerating the rate of deprotonation of substrates with pK_as up to 27.[61] A brief study was undertaken to see if alternative alcohols would improve the yield. Ethanol was used, due to literature precedent,[62] but was found to decrease the yield to 20% (entry 4). When no alcohol additive was used, the yield decreased to 17%, supporting the suggestion for its role as a co-catalyst (entry 5). Variations in pinacol loading from 4 to 2 and 20 mol% were found to give reduced yields (entries 6 and 7).



Entry	Alcohol	Alcohol mol%	T/ °C	Yield/ %
1	pinacol	0.04	60	9
2	pinacol	0.04	80	6
3	pinacol	0.04	r.t	17
4	ethanol	0.04	40	20
5	-	0.00	40	17
6	pinacol	0.02	40	7
7	pinacol	0.20	40	6

Scheme 26: Variation of temperature, alcohol and loading of pinacol.

The concentration of sodium hydroxide was kept constant at 25% w/v, but literature precedent showed concentrations up to 50% w/v have been used successfully for similar reactions.[62] The use of sodium hydroxide at a concentration of 50% w/v was found to have a positive effect on the yield, which rose to 44% (Scheme 27, entry 1). Encouraged by this result, we doubled the amount of sodium hydroxide from 9.5 equivalents at 50% w/v to 19 equivalents at 50% w/v, however, this resulted in a decreased yield of 20% (entry 2). Increasing the catalyst loading from 1 to 5 mol% improved the yield to 57% (entry 3). Further increasing the catalyst loading to 10 mol% gave a reduced yield of 6% (entry 4), which can be accounted for by the increased amount of solid catalyst, resulting in ineffective stirring as the reaction mixture had become a thick paste.

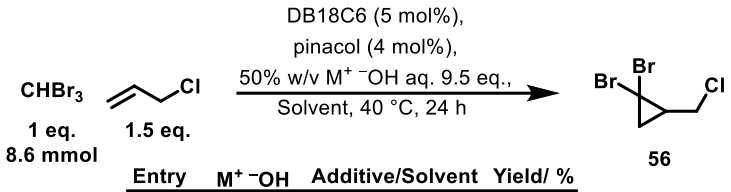


Entry	NaOH (aq)	PTC mol%	Yield/ %
1	9.5 eq., 50% w/v	0.01	44
2	19.0 eq., 50% w/v	0.01	21
3	9.5 eq., 50% w/v	0.05	57
4	9.5 eq., 50% w/v	0.10	6

*Scheme 27: A comparison of the concentration of an aqueous sodium hydroxide solution and PTC loading on the yield of cyclopropane **56**.*

Potassium and lithium hydroxides were tested as bases in place of sodium hydroxide. Given that potassium is known to bind more strongly to DB18C6,[63] this would have been expected to result in improved yields through stronger ion pairing, and the lithium variant to result in a lower yield. Experimentally, potassium hydroxide was observed to give traces of product with lithium hydroxide giving no observable product formation (Scheme 28, entry 1 and 2).

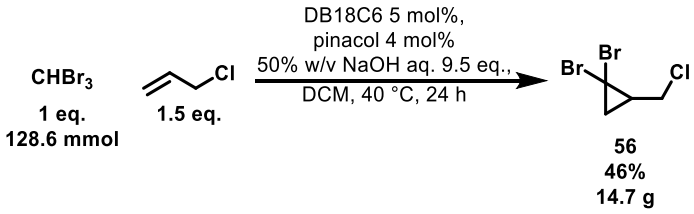
Up to this point, the reactions which produced cyclopropane **56** had always produced a black tarry material, which hindered product isolation and would be problematic on scale. A report by Makosza and co-workers showed that while these reactions commonly produced this thick black tarry material, the use of potassium fluoride dihydrate could prevent its formation in the synthesis of phenyl(trihalomethyl)mercury compounds.[64] Nagarajan and co-workers later published a report supporting Makosza's finding, that the addition of potassium fluoride into the aqueous base solution was beneficial in avoiding the black tar formation, observed in its absence when synthesising *gem*-dibromocyclopropanated sugars.[65] Under our conditions, the addition of potassium fluoride did not alleviate the black tar formation or improve the yield, which dropped to 20% (Scheme 28, entry 3). Finally, it was found that performing the reaction with a DCM co-solvent at a concentration of 1.7 M was beneficial for product isolation. The drawback was that dilution resulted in slightly reduced yields from 57% to 46% (entry 4). A solvent switch to THF was investigated but this was found to give traces of product (entry 5).



Entry	$M^+ {}^-OH$	Additive/Solvent	Yield/ %
1	Li	none	0
2	K	none	0
3	Na	$KF \bullet 2H_2O$	22
4	Na	DCM	46
5	Na	THF	0

Scheme 28: Comparison of different bases and solvents.

After finding the optimal conditions, the reaction was scaled up from 8.58 mmol of bromoform to 128.6 mmol, which yielded 14.6 g of product **56** with a 46% yield (Scheme 29). The yield for this reaction did not prove to be reproducible, with the product generally being isolated in around 30% yield. It was discovered that repeated extraction of the reaction mixture by sonication with pentane[III] provided a more user-friendly and less time-consuming isolation and gave a yield of 45% on a 128.6 mmol scale.

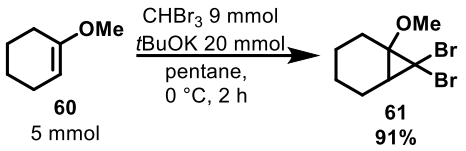


Scheme 29: Optimised conditions for the synthesis of 54 on decagram-scale.

2.3.2. Cyclopropanation of Allyl Chloride with Bromoform using Potassium *tert*-Butoxide

In search of a higher-yielding and more practical synthesis of **56**, an alternative method was briefly investigated. A report from Harayama and co-workers demonstrated the *gem*-dibromocyclopropanation of 1-methoxycyclohex-1-ene **60** using *t*BuOK as a base to form the dibromocarbene, which can react with an alkene to form a *gem*-dibromocyclopropane **61** (Scheme 30).[66]

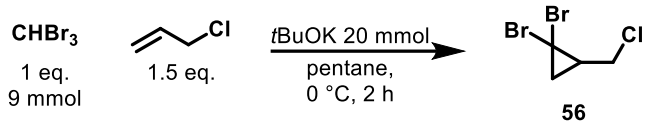
[III] This was developed by Dr. M. Silvi and is included in this thesis to provide a complete picture of the work



Scheme 30: Harayama's cyclopropanation of substituted cyclohexenes.

A reaction based on conditions reported by Harayama and co-workers were modified, using 9 mmol of bromoform, 1.5 equivalents of allyl chloride, 20 mmol of *t*BuOK in pentane (1.6 M) and monitored for the consumption of bromoform. The reaction was observed to be complete within two hours with a yield of 8%[IV] (Scheme 31, entry 1). The counter ion of the base was investigated using both the lithium and sodium analogues, but resulted in either no product formation or a low yield of 4% (entry 2 and 3). The solvent was changed to THF but only traces of product were observed (entry 4). A phase transfer catalyst was also considered, as it may have facilitated the reaction. Due to the success of DB18C6 in previous work, this was selected but only resulted in a 6% yield (entry 5). We found cyclopropane **56** to be light sensitive and so attempted a reaction in the dark, which increased the yield to 12% (entry 6). Suggesting that the product was degrading on exposure to light.

[IV] Yields were calculated from ^{1}H NMR analysis of a crude aliquot of the reaction mixture compared to an internal standard. The internal standard was 1,3,5-trimethoxybenzene.



56

Entry	Variation	yield %
1	2 h reaction time	8
2	*t*BuOLi, 6 h	0
3	*t*BuONa, 6 h	4
4	THF solvent	trace
5	DB18C6 5 mol%	6
6	dark	12
7	0.33 M, dark	23
8	0.65 M, dark	26
9	0.16 M, dark, 3 eq. allyl chloride	21
10	0.16 M, dark, 6 eq. allyl chloride	28
11	neat allyl chloride 15.4 eq., dark	40

Scheme 31: Optimisation of t-BuOK cyclopropanation of allyl chloride.

Increasing the concentration from 0.16 M to 0.33 and 0.65 M led an increased yield of 23 and 26%, respectively (entries 7 and 8). The amount of allyl chloride was then increased to 3 and 6 equivalents at 0.16 M, where the product **56** was observed in 21% and 28% yield (entries 9 and 10), highlighting the importance of concentration and equivalents of allyl chloride for this reaction. Finally, neat allyl chloride was used with 15.4 equivalents and found to give a 40% yield (entry 11). Ultimately, no conditions were found which were an improvement on those previously described (2.2.1) and so further optimisation was not considered.

2.4. Conclusion

The synthesis of cyclopropane **56** has been optimised from 20-27% to 46% yield on a decagram scale under phase transfer catalysed conditions. To optimise the reaction, a range of catalysts, temperatures and sodium hydroxide concentrations were studied. The most significant increase in yield was observed when the concentration of the aqueous sodium hydroxide solution was

increased from 25% w/v to 50% w/v, where the yield improved from 28 to 44% yield. The yield was further improved by increasing the PTC catalyst loading from 1 mol% to 5 mol%, improving the yield from 44% to 57% on small scale. Overall, a yield of 46% of **56** was obtained on a decagram-scale with a user-friendly isolation procedure. An alternative method for the synthesis of cyclopropane **56** was briefly investigated using potassium *tert*-butoxide, but this was lower yielding than the phase transfer catalysis method.

2.5. Future Work

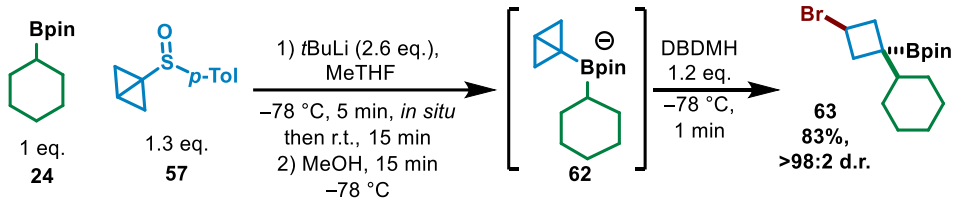
Whilst the work presented herein shows an incremental improvement in yield for the synthesis of cyclopropane **56**, there were limitations encountered along the way. One problem which was repeatedly encountered was the difficulty in isolating the product, from the thick tarry reaction mixture. An improved yield of this crucial reagent for the synthesis of bicyclobutane would be beneficial for further development of the project. Further optimisation of the phase transfer catalysed conditions could study increased reaction times, so bromoform is fully consumed; increased loadings of the catalyst in the presence of DCM, which may further improve the yield; and studying the effect of concentration with respect to DCM under the phase transfer catalysed conditions.

3. Electrophilic Trapping of Bicyclobutyl Boronate Complexes

3.1. Introduction

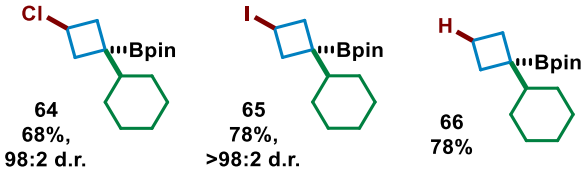
After producing significant quantities of the cyclopropane **56**, it was converted to the bicyclobutyl sulfoxide **57** in good yield on gram-scale (Scheme 22). With bicyclobutyl sulfoxide **57** in hand, an optimisation study by Alex Fawcett found that the bicyclobutyl sulfoxide **57** underwent lithium-sulfoxide exchange on treatment with 2.6 equivalents of *t*BuLi.[55] The lithiated bicyclobutane was directly trapped with a boronic ester *in situ* to give complete boronate complex

62 formation. The addition of methanol at low temperature prior to addition of the electrophile was found to increase both yield and diastereoselectivity. While the exact reason(s) for why methanol improves yield and diastereoselectivity is not known, previous studies have shown similar effects using methanol or 2,2,2-trifluoroethanol (TFE).[49, 67] It has been suggested that the alcohol can act as a hydrogen bond donor to the oxygen atoms on the pinacol boronic ester to stabilise the boronate complex to allow a more selective reaction. Up to this point, the reaction was allowed to run for 1 h at –78 °C followed by 1 h at ambient temperature. However, electrophilic trapping with *N,N'*-dibromodimethylhydantoin (DBDMH) occurred within 1 minute at –78 °C to afford **63** in 83% yield and >98:2 d.r. (Scheme 32).



Scheme 32: Optimised conditions for the reaction of bicyclobutyl boronate complex with an electrophilic source of bromine.

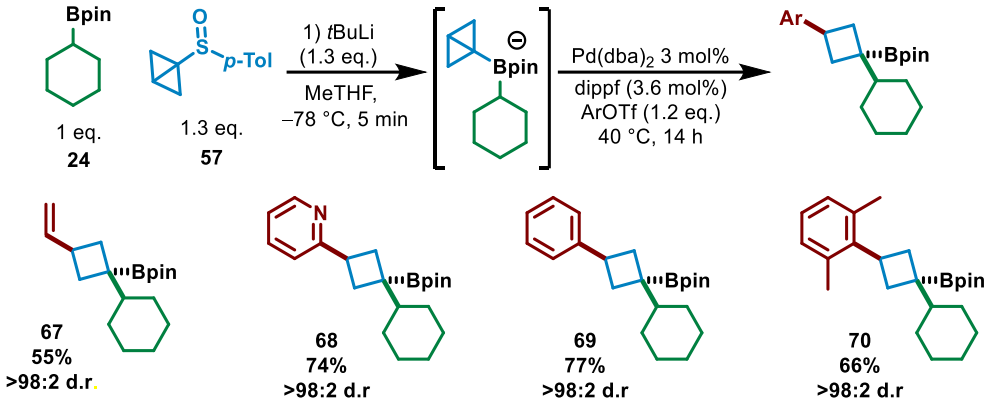
These conditions were used for a brief screen of electrophiles, using *N,N'*-dichlorodimethylhydantoin (DCDMH) and *N,N'*-diiododimethylhydantoin (DIDMH), affording **64** in 68% with 98:2 d.r., and **65** in 78% yield with >98:2 d.r., respectively. Protonation, using methanol, occurred when the reaction was warmed to room temperature for 1 h giving **66** in 78% yield (Scheme 33).



Scheme 33: Chlorination, iodination and protonation of bicyclobutyl boronate complexes.

Inspired by Morken's work on conjunctive cross-coupling (section 1.3.3.), use of electrophilic palladium-aryl complexes was attempted. The reaction was found to afford the products in good yield with excellent diastereoselectivity for a wide variety of C(sp^2)-organotriflates, including vinyl

67, pyridyl **68**, phenyl **69** and 2,6-dimethylphenyl triflates **70** (Scheme 34). This process allows for the coupling of lithiated bicyclobutane, a boronic ester and a C(sp^2)-organotriflate across a C–C σ-bond.



Scheme 34: Conjunctive cross-coupling of bicyclobutyl boronic esters and C(sp^2)-organotriflates.

The relative stereochemistry of the products of this chemistry, shown in Scheme 34, where the electrophile and boron substituent are on the same face of the cyclobutane, has been determined by X-ray crystal structures of several products. Other structures which have not been determined by X-ray crystallography, have been assigned by analogy from analysis of the ^{1}H (on both crude and purified products) and ^{13}C NMR spectra. It was found that, throughout this chemistry, the diastereoisomers have different chemical shifts, and can therefore be used to determine the diastereomeric ratios (Figure 8).[55]

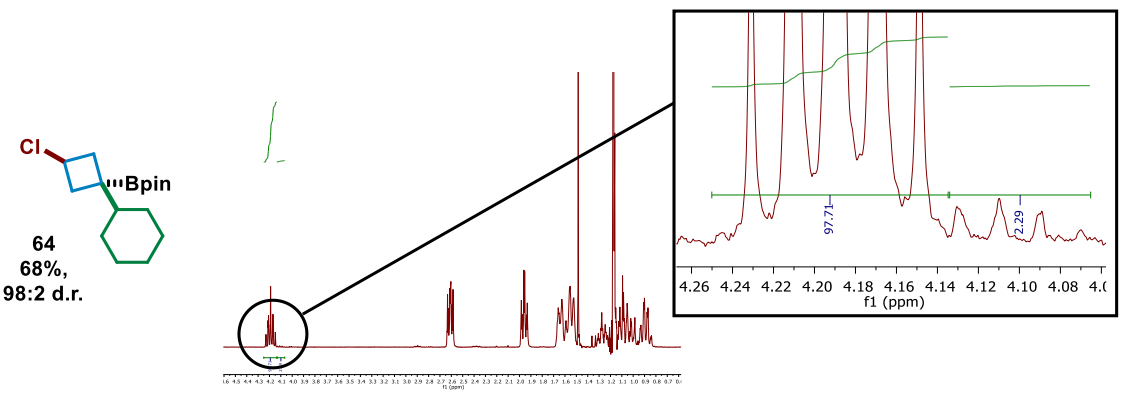


*Figure 8: ^{1}H NMR determination of the diastereomeric ratio of the chlorinated cyclobutane **64**.*

The diastereoselectivity can be rationalised through a mechanism (Figure 9) where a 1,2-metallate rearrangement occurs, when the migrating substituent on boron and the strained C–C σ-bond align antiperiplanar to each other (A). The electrophile can approach from either the *exo* or *endo* face of the boronate complex, but the *endo* face is sterically hindered by the pinacol boronic ester, thus favouring *exo* attack (B). Moreover, as the central 1,3-bond of bicyclobutane has high p-orbital character, substantial electron density projects from the *exo* face of the β-carbon which favours *exo* attack (C). Overall, the high diastereoselectivity observed throughout this chemistry suggests a concerted process, whereby the 1,2-metallate rearrangement and cleavage of the strain C–C bond occur simultaneously.

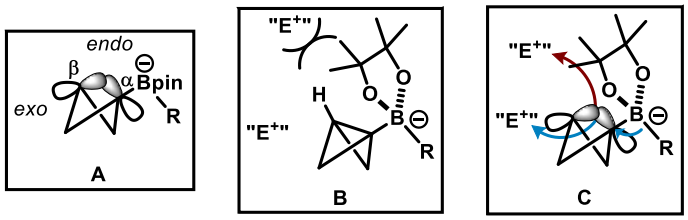


Figure 9: Rationale for diastereoselectivity. A) The exo and endo face of bicyclobutane. B) Steric hindrance when the electrophile approaches from the top face. C) Electronic density which protrudes from the β-carbon.

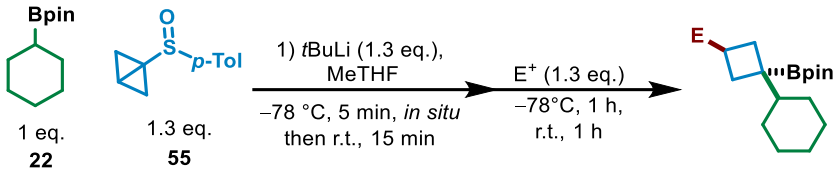
3.2. Project Aim

At this point, a small range of electrophiles had been demonstrated to be successful with bicyclobutyl boronate complexes to form substituted borylated cyclobutanes, which are potentially useful units in chemical synthesis and medicinal chemistry (sections 1.1. and 1.2.). We therefore wanted to expand the range of electrophiles that can be used in the described chemistry to make a variety of structures and include a variety of other functional group and, if required, undertake further optimisation to improve the yield and/or diastereoselectivity.

3.3. Results and Discussion

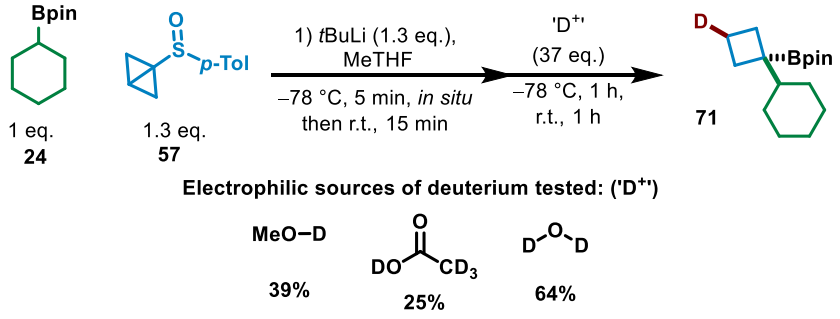
Previously, conditions for this chemistry used a large excess of *t*BuLi (2.6 eq) and methanol, which may react with the electrophilic species. To avoid potential problems, and make the reaction

conditions more general, we used 1.3 equivalents of the *t*BuLi, for complete lithium-sulfoxide exchange, and omitted the alcohol additive (Scheme 35).



Scheme 35: Standard conditions for electrophilic trapping.

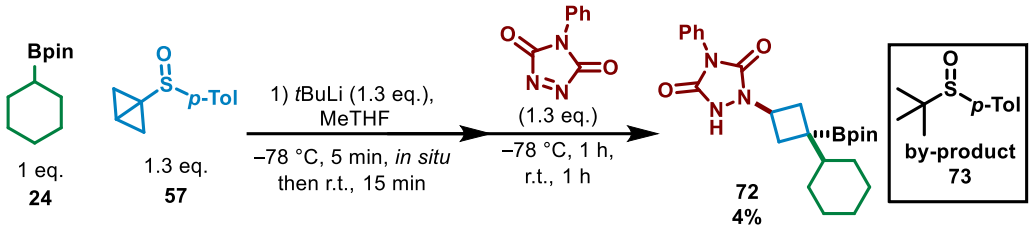
Initially, we wanted to deuterate the cyclobutane ring, as this isotope is important for both mechanistic studies[68] and in medicinal chemistry.[69] As protonation had previously been achieved, we suspected deuteration would also be possible. Initially, deuteration with methanol-d_4 gave 39% of the product **71**, which was a surprise given that protonation occurred with 78% yield (Scheme 36). A possible explanation for a lower yield of deuterated product **71** could be that, as the isotope is heavier, the O–D bond is stronger, and hence less acidic. Therefore, we reasoned that a more acidic electrophilic source of deuterium would increase the yield. Acetic acid-d_4 was tested; surprisingly, only 25% yield was achieved. This suggests that the acidity of methanol-d_4 was not the cause of the lower yield. Instead, it suggests that some protonation for **66** occurs during the work-up procedure. Thus, deuterated water was used, which afforded the deuterated cyclobutane **71** in 64% yield with 95% deuterium incorporation. The diastereoselectivity could not be determined due to overlap of the key signals involved.



Scheme 36: Reaction of the bicyclobutyl boronate complex with electrophilic deuterium sources.

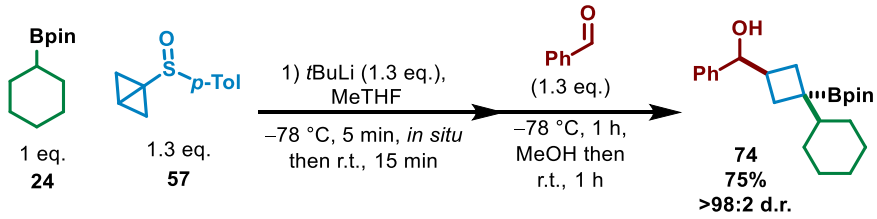
Some reactions of substituted bicyclobutanes have been explored with dienophiles. The reports by Dougherty[70] and Amey[71] have shown bicyclobutanes to undergo a cycloaddition reaction with

strong dienophiles such as 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione. Whilst our work was not focused on using this as a dienophile, the nitrogen may be suitable for nucleophilic attack by the bicyclobutyl boronate complex. The reaction gave **72** with a 49% yield with 60:40 d.r. by ^{1}H NMR analysis of an aliquot of the crude reaction mixture containing an internal standard (Scheme 37). However, an isolated yield of 4% of a single diastereoisomer was the result of **72** having a similar retention factor to the sulfoxide by-product **73**. A higher yield may be obtained by oxidising the boronic ester and isolating the corresponding alcohol, however, this removes the boronic ester functional handle.



Scheme 37: The reaction of bicyclobutyl boronate complex with 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione

When benzaldehyde was used as an electrophile, this afforded **74** in 63% yield with a >98:2 d.r. under standard conditions (Scheme 38). Anhydrous methanol was added before the electrophile as for the bromination conditions, resulting in a slightly improved 66% yield of **74**. Alternatively, methanol was added after benzaldehyde had reacted for 1 h at –78 °C, and we observed that the yield increased to 75% with a >98:2 d.r. (Scheme 38).



Scheme 38: Reaction of the nucleophilic bicyclobutyl boronate complex with benzaldehyde.

With these modified conditions in hand, we tested the scope of aldehydes with different steric and electronic properties and discovered it to be broad (Figure 10). Propanal gave **75** in 79% with >98:2 d.r. which showed that the methodology is not limited to aryl aldehydes. Initially, pivalaldehyde

gave **76** in a moderate yield of 50% with >98:2 d.r., but this was improved to 70% when methanol was omitted. This implies that the steric bulk of the aldehyde slowed its reaction with bicyclobutyl boronate complex so the remaining boronate complex was protonated by methanol. Cinnamaldehyde was tested and afforded **77** in 73% yield with a d.r. of >98:2. Both *p*-trifluoromethyl and *p*-methoxy benzaldehydes both gave good yields and excellent d.r.s of **78** in 70% with 97:3 d.r. and **79** in 64% with >98:2 d.r., respectively. A heteroaromatic, picolinaldehyde, was also successful and gave **80** in 55% yield with a d.r. of >98:2.

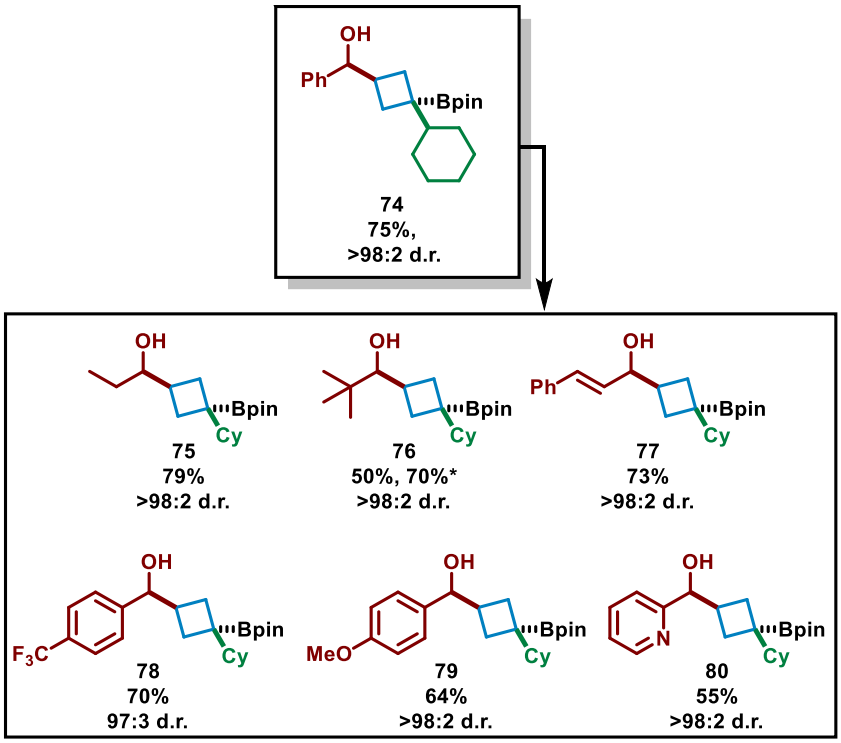
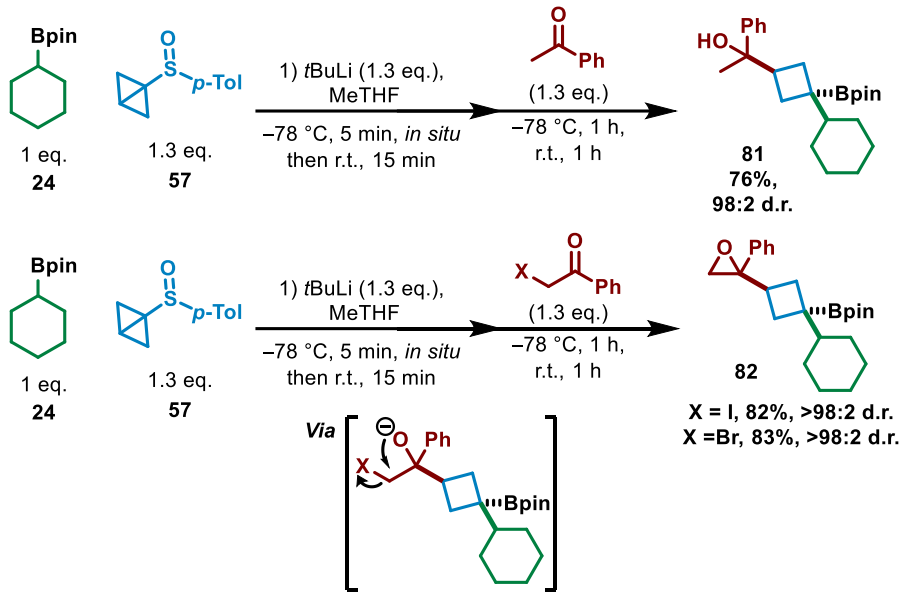


*Figure 10: Products from the reaction of the bicyclobutyl boronate complex with a diverse range of aldehydes. Reaction conditions are shown in Scheme 38. *No methanol was added.*

As aldehydes had proven successful under the reaction conditions, it was envisaged that a ketone, a less electrophilic carbonyl, may further challenge the reactivity of the bicyclobutyl boronate complex. Acetophenone was used and found to afford **81** in 76% yield with 98:2 d.r. (Scheme 39). As a ketone had been successful, we considered using an α-haloacetophenone which could form an a tetrahedral intermediate from nucleophilic addition to the carbonyl, which could undergo intramolecular cyclisation to deliver an epoxide. Indeed, this reactivity was observed, and epoxide

82 was formed in 82% yield with >98:2 d.r., using iodoacetophenone, with similar results observed for the commercially available bromoacetophenone (Scheme 39).



Scheme 39: Electrophilic trapping of the bicyclobutyl boronate complex with a ketone and α-haloketones.

Due to the positive results obtained with aldehydes and ketones, we next decided to study *N*-protected imines as electrophiles. Initially, *N*-benzylidenebenzenesulfonamide was tested under the original conditions. A 76% yield of **83** was obtained with a good d.r. of 81:19 (Figure 11). Anhydrous methanol was added before the imine to try to improve the diastereoselectivity, which resulted in a 71% ^{1}H NMR yield with an improved d.r. of 87:13. To further increase the diastereoselectivity, TFE was tested as this had previously been successful with vinyl-boronate chemistry,[49] affording **83** in 73% yield with a d.r. of 93:7. As the TFE had been successful, 1,1,1,3,3,3-hexafluoro-2-propanol, known to participate in strong hydrogen bonding,[72] was also tested to see if this would further increase the diastereoselectivity. Unfortunately, this decreased both yield and d.r. to 61% and 76:24, respectively. To further improve the result, we then considered whether alternative *N*-protecting groups would modify the reactivity of the imine. Whilst the Boc protected imine failed to give any observable product, the phosphoramide, without an additive, gave **84** in 36% yield but with a good d.r. of 90:10. The addition of methanol resulted in improved yield

and d.r of 54% and 93:7. Trifluoroethanol resulted in a suppressed yield of 38%, yet it further improved the diastereoselectivity to give a d.r. of 97:3.

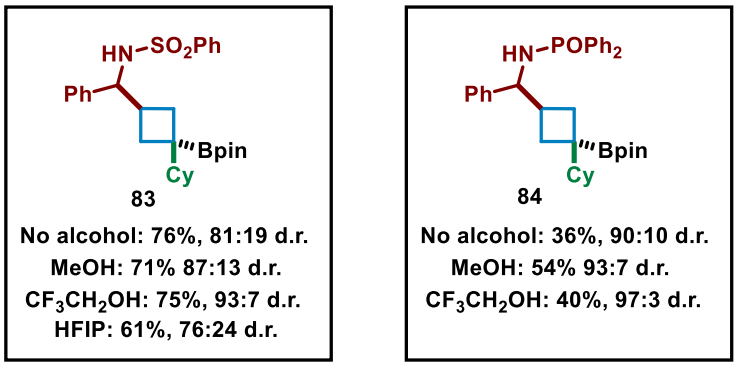


Figure 11: Comparison of electrophilic trapping of the bicyclobutyl boronate complex with different imines and alcohol additives. Reaction conditions are shown in Scheme 35, with the addition of alcohol at –78 °C, 15 min before the electrophile was added.

To further test the carbonyl class, benzoyl chloride was subjected to the reaction conditions and gave **85** in a yield of 88% with 98:2 d.r., but an unknown side product (C) was observed in the ^{1}H NMR after flash column chromatography (with A and B being the major and minor diastereoisomers, respectively) (Figure 12).

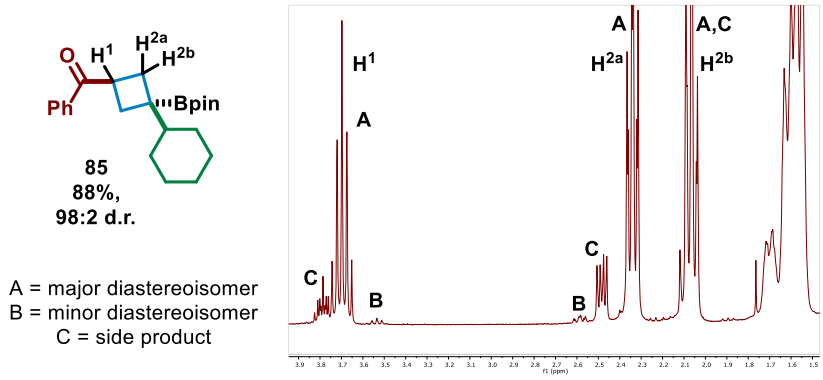


Figure 12: The product of the reaction between benzoyl chloride and bicyclobutyl boronate complex, and the presence of an unknown side product observed by ^{1}H NMR.

When methyl chloroformate was subjected to the reaction conditions, it was found to give traces of product. An alternative chloroformate, 2,2,2-trichlorocarbonyl chloride (TrocCl), gave **86** in 57% yield with a 96:4 d.r., however, this again contained a significant amount of the unknown side product (C) (Figure 13). In an attempt to determine the structure of the side product, we used 2-isopropyl pinacol boronic ester, which would reduce the number of peaks in the ^{1}H NMR

spectrum. Whilst the reaction was successful, giving **87** in 60% yield alongside the unknown side product, analysis of the ^{1}H, COSY, HSQC and HMBC spectra failed to aid our structural determination of the side product. Both dimethyl carbamoyl chloride and di-*tert*-butyl dicarbonate resulted in no observable product by ^{1}H NMR analysis of an aliquot of the crude reaction mixture.

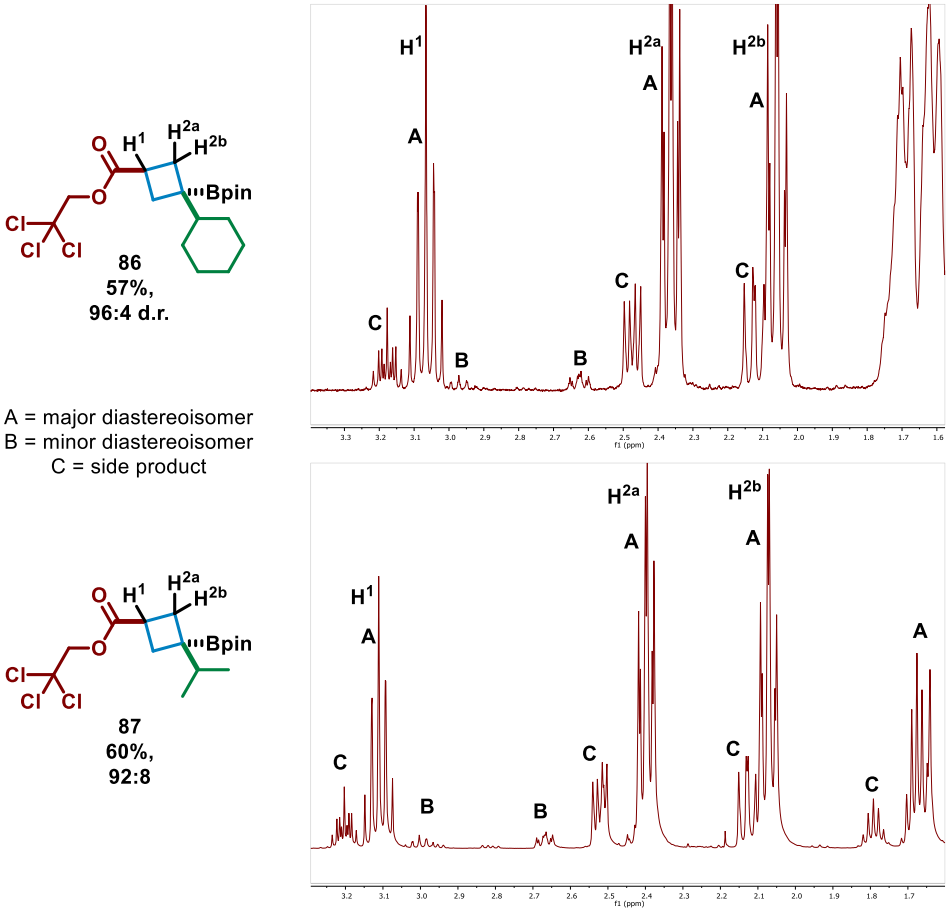
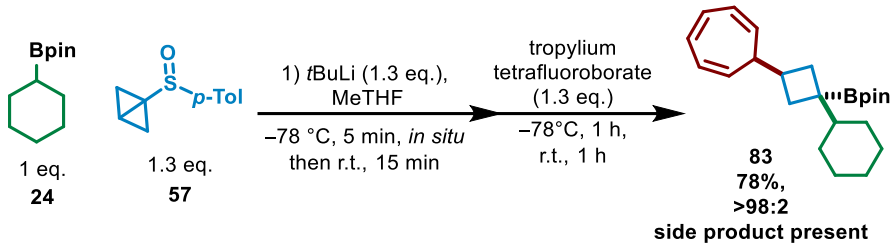


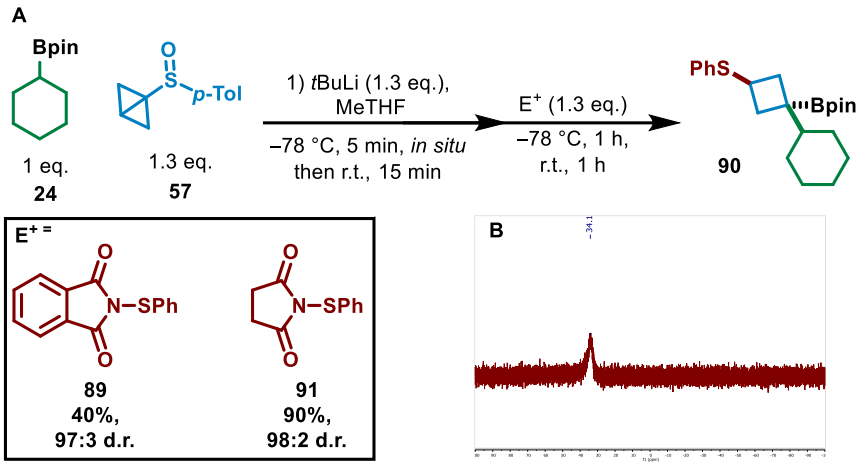
Figure 13: The product of the reaction between 2,2,2-trichlororoethoxycarbonyl chloride and bicyclobutyl boronate complex with the side product shown in the ^{1}H NMR.

As tropylium tetrafluoroborate had been successful in previous nucleophilic boronate chemistry (section 1.3.5), it was reasoned this could also be a successful electrophile in this chemistry. Whilst tropylium tetrafluoroborate was found give **83** in 78% yield with >98:2 d.r. (Scheme 40), the side product again appeared alongside the material.



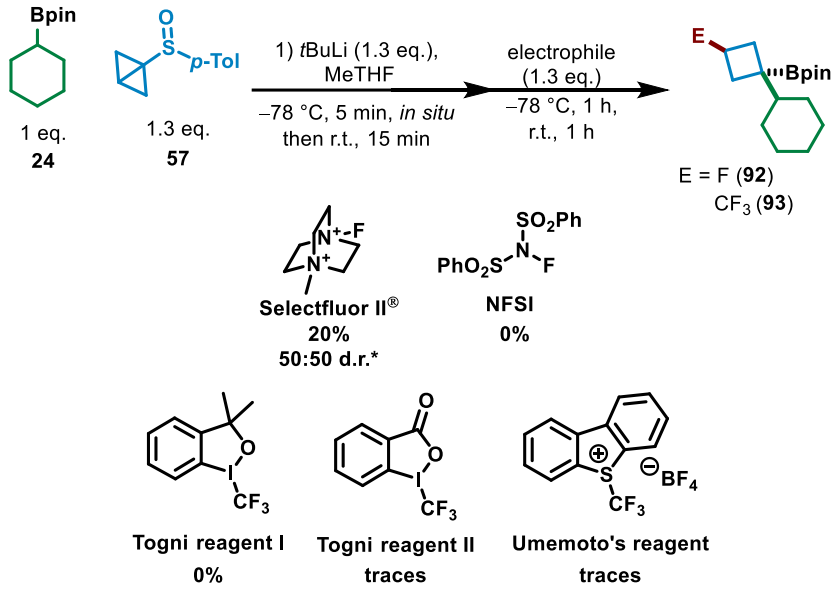
Scheme 40: Reaction of the nucleophilic bicyclobutyl boronate complex with tropylium tetrafluoroborate.

In order to incorporate a sulfur based electrophile, 2-(phenylthio)isoindoline-1,2-dione **89** was tested under standard conditions to give **90** in 40% yield with a d.r. of 97:3 (Scheme 41A). However, like some previous electrophiles, the side product was present. With the objective of inhibiting side product formation, TFE and methanol were added to separate reactions before the electrophile. However, the protonated product **66** was observed in both cases, which suggests that the sulfur electrophile is reacting at temperatures above –78 °C. The reaction was attempted at –40 and –78 °C for 16 h to observe whether the side product formation would be inhibited at these low temperatures, however, side product still formed in both cases. To check whether borinic ester was forming via an *O*-migration, the isolated product was subjected to ^{11}B NMR analysis. This showed a characteristic signal for the boronic ester at 34 ppm and no other peaks (Scheme 41B), if borinic ester had been present a peak at around 50 ppm would have been present. Finally, a different electrophilic phenyl sulfide equivalent, phenylthiosuccinimide **91**, was used to afford the product **90** in 90% yield with a 98:2 d.r., but still contaminated with the side product. It should be noted that, in each case, the side products appear to contain the electrophiles, as ^{1}H NMR analysis of all samples containing the unknown side products, show different chemical shifts for different electrophiles. We analysed the product **90** by GC-MS, which showed that the side product had the same molecular weight as the product and an identical fragmentation pattern. Overall, the data for the side product suggests it is a constitutional isomer of the product.



Scheme 41: A) Reaction of the bicyclobutyl boronate complex with electrophilic sources of sulfur. B) The ^{11}B NMR analysis of the isolated product which shows a single peak characteristic of the boronic ester.

Fluorinated molecules are commonly used in medicinal chemistry to improve biological activity of potential drugs for several reasons such as increasing the lipophilicity, or using a C–F bond to make a molecule stable under physiological conditions, where a C–H bond may be labile.[73] Fluorination was unsuccessful using Selectfluor II® or NFSI (Scheme 42) under standard conditions. Alternative conditions, optimised for use with nucleophilic boronate complexes, resulted in 20% yield of **92** with a d.r. of 50:50 using Selectfluor II, however, this contains an unknown impurity.[53] Whilst no further conditions were tested, alternative co-solvents may lead to yield and d.r. improvements.[74]

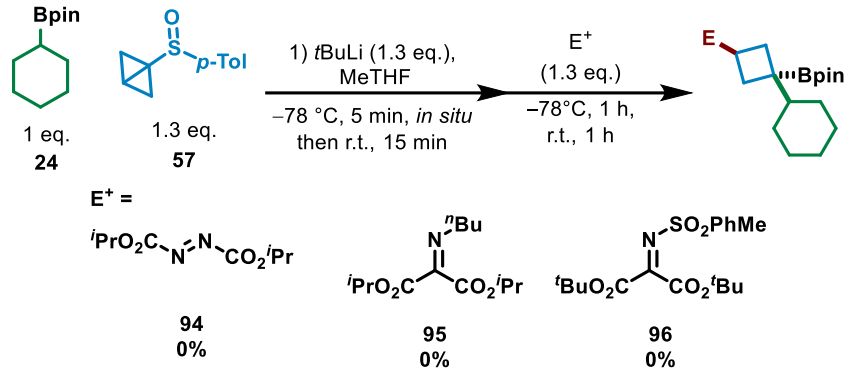


*Scheme 42: Reaction of the bicyclobutyl boronate complex with electrophilic fluorinating and trifluoromethylating reagents and their structures. *Alternative conditions were used based on a literature procedure,[53] involving a solvent switch to MeCN and addition of styrene.*

The trifluoromethyl group is an important structural unit, which was present in more than ten drugs in phase II and III clinical trials in 2016.[75] Commercial electrophilic sources of the trifluoromethyl group were tested with the bicyclobutyl boronate complex and we found that, whilst Togni I and Umemoto's reagent showed unproductive reaction under standard conditions, Togni II gave a trace of product (Scheme 42). Trifluoroiodomethane-DMSO was also tested but only protonated product was observed. This is likely a result of the DMSO containing water. A solvent switch from MeTHF to MeCN after boronate complex formation was attempted to dissolve Togni II, but no product was observed by ^{1}H NMR analysis of an aliquot of the crude reaction mixture. A reaction was tried using reduced equivalents, 1.0 instead of 1.3, of Togni II as this had been advantageous in related work,[76] but only traces of product were detected in this instance. Due to the low yield, a longer reaction time, 16 h, at –78 °C was used to see if a slow reaction was the cause of the low yield, again, traces of product were found. The reaction was then tested at –40 °C for 16 h which afforded traces of **93**. Due to literature precedent with Umemoto's reagent,[67] a solvent switched from MeTHF to MeCN, after boronate complex formation was attempted, yet only traces of **93** were formed. Whilst this remains an important electrophile, we decided that further investigation should be deferred as only traces of product had been obtained.

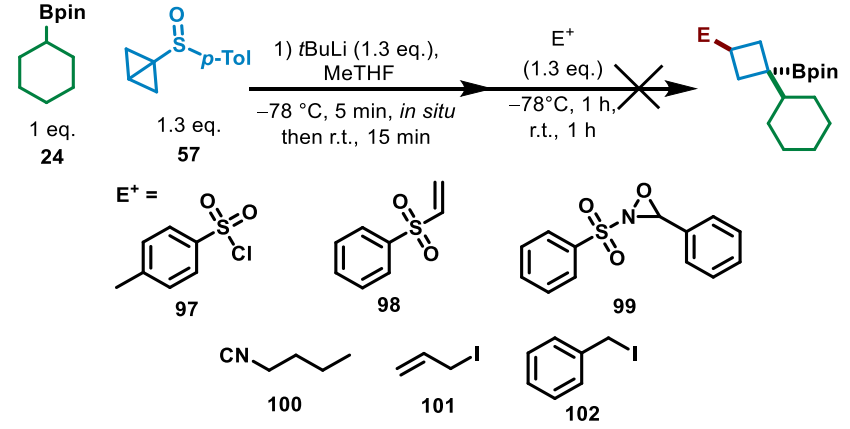
A nitrogen-containing electrophile, diisopropyl azodicarboxylate (DIAD) **94**, was tested yet we found no observable product (Scheme 43), which contrasts with the previous nucleophilic boronate complex chemistry where it was found to be a successful electrophile (section 1.3.5.) and 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione which reacted with the bicyclobutyl boronate complex. Recently, Kurti and co-workers established a range of singly and doubly electrophilic aminating reagents which underwent nucleophilic attack at the nitrogen atom with a range of Grignard and organolithium nucleophiles.[77] After synthesising both singly electrophilic **95** and doubly electrophilic **96** reagents, they were tested under standard conditions but no product was observed

in the ^{1}H NMR of an aliquot of the crude reaction mixture and no other identifiable species were found after flash column chromatography.



Scheme 43: Reaction of the bicyclobutyl boronate complex with nitrogen-containing electrophiles.

Continuing the electrophile screen, tosyl chloride **97**, vinyl phenylsulfone **98**, 3-phenyl-2-(phenylsulfonyl)oxaziridine **99** and *n*-butylisonitrile **100** were also tested (Scheme 44). However, no product was observed by ^{1}H NMR analysis of an aliquot of the crude reaction mixture in all cases. Allyl **101** and benzyl **102** iodides were promising candidates given the excellent leaving group they both possess. Further, allyl iodide could react at either the vinyl position in an S_N2' fashion or directly via an S_N2 mechanism. However, no product was observed for either electrophile.



Scheme 44: The reaction of bicyclobutyl boronate complex with several electrophiles.

While we do not yet fully understand why some electrophiles do react whereas others do not, our ability to predict reaction outcomes would be significantly enhanced by continued investigation,

both experimentally and theoretically. Yet some inferences can still be drawn from the data collected. For example, the results obtained so far show that the bicyclobutyl boronate complex has not yet partaken in Michael addition to unsaturated systems, as observed in the case of vinyl sulfone, which is surprising given the π-type character of the strained C–C σ-bond which has significant literature precedent.[9] Other Michael acceptors, such as methyl acrylate, are yet to be tested.

3.4. Conclusion

We have tested a range of electrophiles in a reaction with a bicyclobutyl boronate complex, which has resulted in the formation of novel 1,1,3-trisubstituted borylated cyclobutanes. Specifically, the products have been afforded in good yield and with high diastereoselectivity when treated with deuterium oxide, imines, ketone, α-iodo- and α-bromoacetophenones, and a wide range of aldehydes. Other electrophiles, such as selectfluor II®, Togni II, and 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione gave low yields or traces of their respective product with more variable diastereoselectivities. During the course of this investigation, we have found that electrophiles which react can be improved with methanol or TFE addition if there are no chemoselectivity issues.

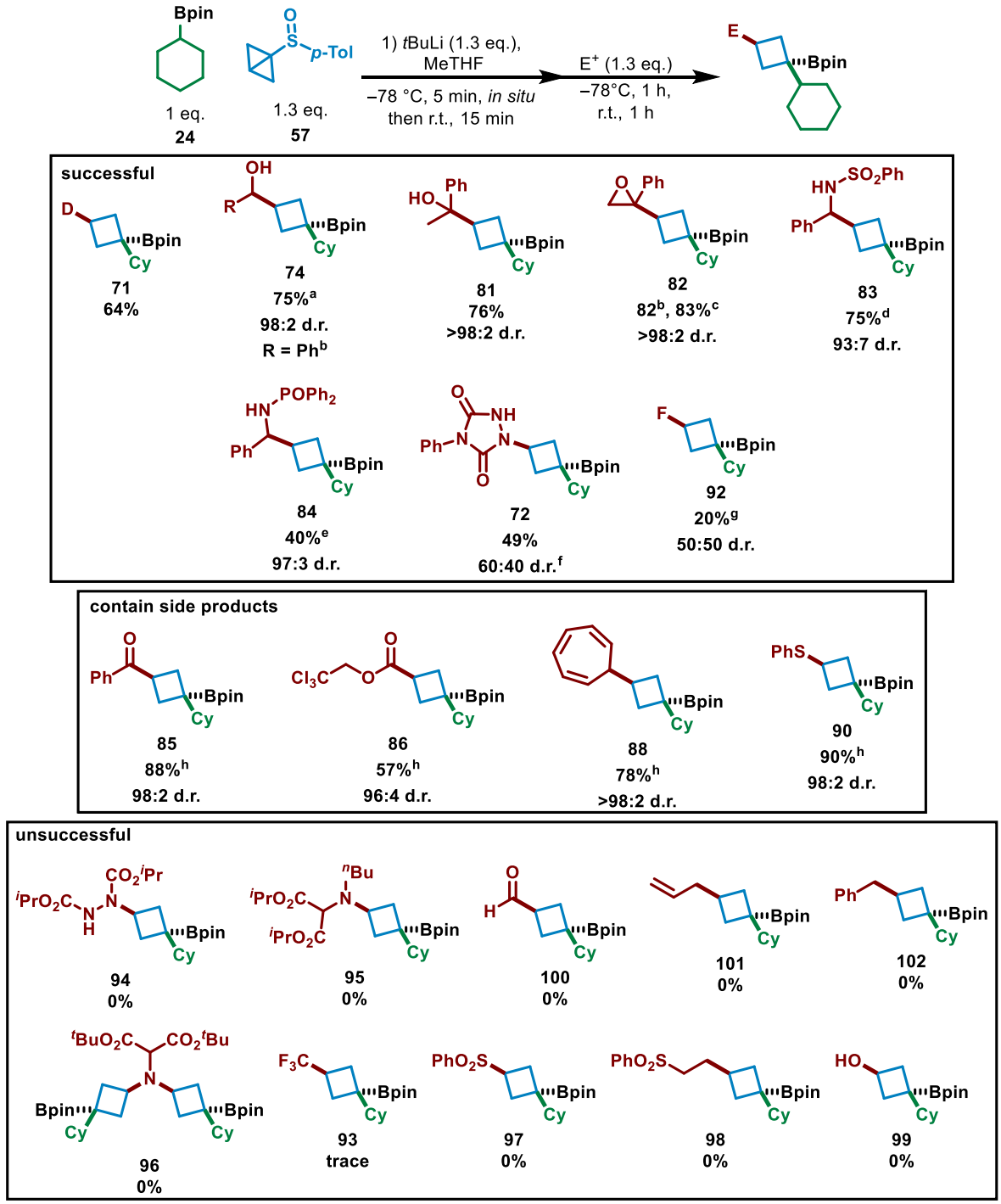


Figure 14: A complete list of electrophiles tested. [a] see Scheme 38 for conditions, see Figure 10 for alternative R groups. [b] using α-bromoacetophenone. [c] using α-iodoacetophenone. [d/e] see Figure 11 and the related text for reaction conditions. [f] this was determined by analysis of an aliquot of the crude reaction mixture. [g] the product isolated with an unknown impurity. [h] the products are contaminated with side products

3.5. Future Work

Further investigation could be focused on several alternative areas such as more experimental work to improve the diastereoselectivity. For instance, the diastereoselectivity of the reaction of

bicyclobutyl boronate complex with acetophenone may be increased with the addition of methanol or TFE. Alternatively, the electrophile scope could be further expanded by trialling electrophiles which have not yet been studied, such as methyl acrylate and an electrophilic source of the trifluoromethyl thiol unit.[78] The structure of the persistent side product, which contains the electrophile and a quaternary carbon, should also be determined. If its formation can be suppressed, to allow a clean reaction, several electrophiles will react to give uncontaminated product such as acid chlorides, chloroformates, tropylium tetrafluoroborate and the electrophilic phenyl sulfide equivalent.

Outside of the electrophile scope, the boronic ester scope remains to be explored which should extend to primary, secondary, tertiary and aromatic substituents as observed in previous chemistry.[44,49,53,54] Some enantiopure boronic esters should be included and their enantiospecificity measured to confirm the 1,2-metallate rearrangement pathway is occurring stereospecifically at the migrating carbon. Finally, a selection of boronic ester transformations would highlight the power of this chemistry by incorporating a range of other functional groups (Figure 15).

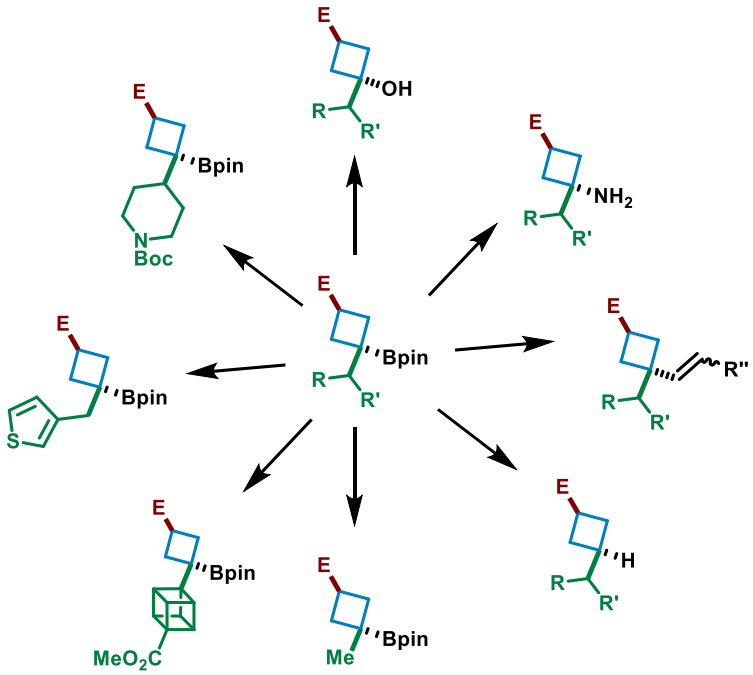


Figure 15: Possible variations of the migrating group or transformations of the boronic ester.

4. General Conclusion

The synthesis of the 1,1-dibromo-2-(chloromethyl)cyclopropane has been optimised under phase transfer catalysis on an 8.58 mmol scale, to form the cyclopropane **56** in 46% yield. The reaction scale was increased to 128.6 mmol of bromoform, to afford 14.6 g of the cyclopropane **56** in 46% yield. This is an important improvement over previously reported conditions,[58] which were found to be difficult to reproduce. This key starting material is now more readily available for the preparation of the bicyclobutyl sulfoxide **55** reagent.

The bicyclobutyl boronate complex has been found to successfully react with a variety of previously unexplored electrophiles, including aldehydes **74 - 80**, ketones **81** and α-haloketones **82**, which react with good yields and excellent diastereoselectivities. A range of aldehydes reacted successfully including alkyl, sterically encumbered alkyl, allyl, electron-poor aromatic, electron-rich aromatic and heteroaromatic aldehydes. Imines **83 - 84** have also reacted successfully, again with high levels of diastereoselectivity. Deuteration **71** of the bicyclobutyl boronate complex was also achieved. The work presented herein has shown the bicyclobutyl boronate complex can react with several different electrophiles to generate 1,1,3-trisubstituted cyclobutanes with good yields and diastereoselectivities. This methodology could represent an attractive route for the modular synthesis of cyclobutanes.

5. Supplementary Information

5.1. General Experimental Information

Reagents and Solvents

All air- and moisture-sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere using standard Schlenk manifold technique. Anhydrous solvents were commercially supplied or provided by the communal stills of the School of Chemistry, University of Bristol, and were dried using a purification column composed of activated alumina and stored over thoroughly dried 3 Å mol sieves.[79]

Cyclohexyl pinacol boronic ester **22** [CAS: 87100-15-0] was purchased from Alfa-Aesar and was purified by flash column chromatography (SiO_2; 95:5 pentane:Et_2O) before use. Anhydrous 2-methyl tetrahydrofuran [CAS: 96-47-9] was purchased from Sigma-Aldrich and used as received. *tert*-Butyl lithium (1.7 M in pentane) [CAS: 594-19-4] was purchased from Sigma-Aldrich and used as received. Methyl lithium (1.6 M in Et_2O) [CAS: 917-54-4] was purchased from Acros and used as received. The molarity of organolithium solutions were determined by titration using *N*-benzyl benzamide as an indicator.[80] The aldehydes used were all purified by Hickmann distillation prior to use. Electrophiles which were not commercially available were synthesised according to literature procedures: α-iodoacetophenone,[81] *N*-benzylidene-*P*,*P*-diphenylphosphinic amide,[82] 1-(phenylthio) pyrrolidine-2,5-dione **86**,[83] di-*tert*-butyl 2-(butylimino)malonate and diisopropyl 2-(tosylimino) malonate (electrophilic imines **91** and **92**).[77] All other reagents were purchased from various commercial sources and used as received.

Chromatography and Data Analysis

Flash column chromatography was carried out using Sigma-Aldrich silica gel 60 (40 – 63 μm). All reactions were followed by thin-layer chromatography (**TLC**) when practical, using Merck Kieselgel

60 F254 fluorescent treated silica, which was visualised under UV light, or by staining with either anisaldehyde or an aqueous solution of $KMnO_4$ followed by heating.

^{1}H, **^{13}C,** **^{19}F and ^{31}P NMR** spectra were recorded using Jeol ECS 400 MHz, Bruker Nano 400 MHz and Varian VNMR 400 MHz spectrometers. Chemical shifts (δ) are given in parts per million (ppm) with signal splittings reordered as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn) and multiplet (m). Coupling constants (J) are given in Hertz (Hz), rounded to the nearest 0.1 Hz. The ^{1}H NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons, assignment). NMR assignments are made according to spin systems, using two-dimensional NMR spectroscopy (COSY, HSQC, HMBC), where appropriate, to assist the assignment. Where an assignment could not be made unambiguously, no assignments are given. ^{13}C signals adjacent to boron are generally not observed due to quadrupolar relaxation.

High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics MicrOTOF II by Electrospray Ionisation (ESI) or on a VG Micromass Autospec (Triple-sector) by Electronic Impact (EI) or on a Bruker Daltonics UltrafleXtreme (MALDI).

IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR as a thin film, if an oil, or in the solid state, if solid. Only selected absorption maxima (ν_{max}) are reported.

Melting points were recorded in degrees Celsius (°C) using a Kofler hot-stage microscope apparatus.

Gas Chromatography (GC) was performed on an Agilent 7890A using an Agilent HP-5 column (15 m x 0.25 mm x 0.25 μm).

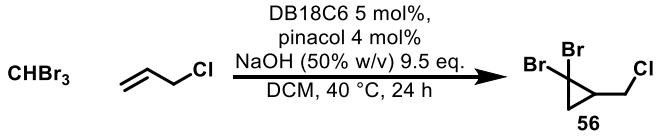
GC-MS was performed on an Agilent 6890 Series GC and 5973 detector using a HP-5MS UI column (15 m x 0.25 mm x 0.25 μm).

Naming of Compounds

Compound names are those generated by ChemBioDraw 13.0 software (PerkinElmer), following the IUPAC nomenclature.

5.2. General Experimental Procedures

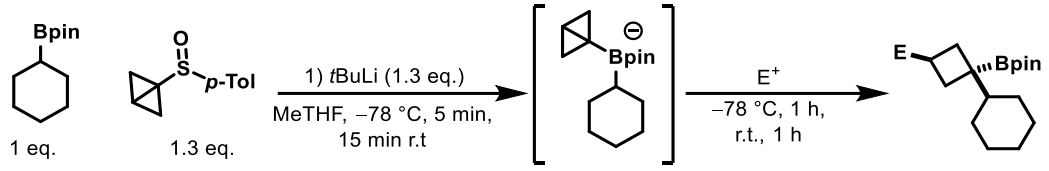
5.2.1. Synthesis of *gem*-1,1-Dibromo-2-(chloromethyl)cyclopropane (56)



A 250 mL flask was charged with dibenzo-18-crown-6 ether (2.14 g, 5.90 mmol, 5 mol%), pinacol (608 mg, 5.20 mmol, 4 mol%), bromoform (11.3 mL, 32.5 g, 129 mmol, 1.00 eq.), DCM (75 mL) and allyl chloride (21.0 mL, 19.7 g, 257 mmol, 2.00 eq.). A concentrated sodium hydroxide solution[A] (50% w/v, 48.9 g in 49.0 mL of water, 9.5 eq.) was then added to the stirring solution before an air condenser with a septum and nitrogen balloon was quickly attached to the flask. This solution was then heated at 40 °C for 24 h. The reaction was allowed to cool to ambient temperature and a portion (approximately a third) of the solution was extracted with pentane (3× 200 mL) by sonication (2 min) and, after distinct layers had formed, the top layer[B] is decanted through a thick pad of Celite on a thin pad of silica. The bottom layer is then extracted twice in the same manner and this procedure is performed for the rest of the crude reaction mixture. The combined solutions were then concentrated under reduced pressure to give an orange oil. Pentane was added to the oil until no further precipitate was observed and then filtered over a layer of sand and silica plug with pentane rinsing. If no bromoform is present[C] the solution[D] can be concentrated to dryness to give the product. If bromoform is present, the material should be purified by flash column chromatography (pentane) to give the title compound **56** as a dense colourless oil (14.6 g, 46%). **Notes:** A) this solution is most effectively made by grinding the sodium hydroxide pellets to a fine powder and adding this to a vigorously stirring water at 0 °C (caution: exotherm), then allowing the solution to stir at room temperature until the sodium hydroxide has fully dissolved. B) the top layer

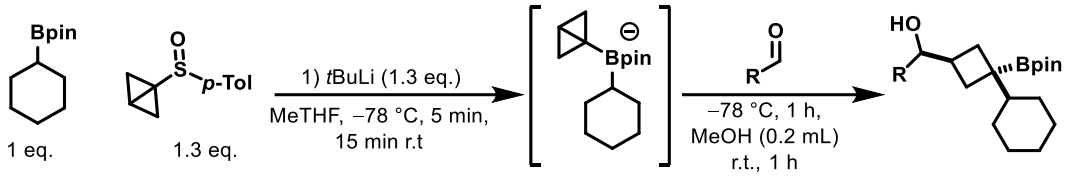
should be a pale-yellow solution where the bottom layer is a thick black tar. It is important not to get any tar onto the Celite filter this can cause it to clog. C) most conveniently observed by ^{1}H NMR or by GC-MS. D) The product is slightly light sensitive so it should be isolated with minimal exposure to light and should be stored under argon in a freezer. **TLC:** R_f = 0.65 (hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.65 (d, J = 7.5 Hz, 2H, CH_2Cl), 2.08 – 2.00 (m, 1H, CH), 1.93 (dd, J = 10.3, 7.6 Hz, 1H, CH_aH$_b$), 1.48 (app.t, J = 7.5 Hz, 1H, CH$_a$$H_b$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 46.3 (CH_2Cl), 32.3 (CH), 29.1 (CH_2), 25.8 (CBr_2) ppm. All other data matches that reported in the literature.[84]

5.2.2. General Procedure A: Electrophilic Trapping of the Bicyclobutyl Boronate Complex



General Procedure A: *tert*-Butyl lithium (in pentane, 0.31 mmol, 1.30 eq.) was added dropwise to a solution of bicyclobutyl sulfoxide **57** (60 mg, 0.31 mmol, 1.30 eq.) and cyclohexyl pinacol boronic ester **24** (50 mg, 0.24 mmol, 1.00 eq.) in MeTHF (2.1 mL) at –78 °C (dry ice/acetone) and allowed to stir for 5 min. After removing the cooling bath, the reaction was allowed to warm to ambient temperature for 15 min before being cooled back to –78 °C for 2 min before addition of the electrophile (0.31 mmol, 1.30 eq.) and left to stir for 1 h. After being allowed to warm to ambient temperature for 1 h, the solution was transferred to a 28 mL vial containing H_2O (5 mL) and NH_4Cl (5 mL) (saturated aqueous solution of NH_4Cl) and the flask rinsed with Et_2O (15 mL). The vial was then sealed and shaken vigorously and the top layer carefully collected using a pipette and placed into another 28 mL vial. The aqueous layer was extracted with Et_2O (2× 7 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. At this point a crude ^{1}H NMR and GC was taken to determine the presence and d.r. of product. The crude residue was then directly purified by flash column chromatography (SiO_2) to yield the desired cyclobutane.

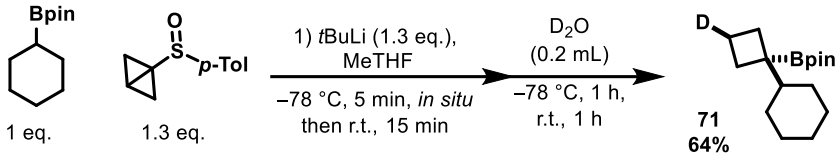
5.2.3. General Procedure B: Electrophilic Trapping of the Bicyclobutyl Boronate Complex



General Procedure B: *tert*-Butyl lithium (in pentane, 0.31 mmol, 1.30 eq.) was added dropwise to a solution of bicyclobutyl sulfoxide **57** (60 mg, 0.31 mmol, 1.30 eq.) and cyclohexyl pinacol boronic ester **24** (50 mg, 0.24 mmol, 1.00 eq.) in MeTHF (2.1 mL) at –78 °C (dry ice/acetone) and allowed to stir for 5 min. After removing the cooling bath, the reaction was allowed to warm to ambient temperature for 15 min before being cooled back to –78 °C for 2 min before addition of the aldehyde (0.31 mmol, 1.30 eq.) and left to stir for 1 h. Methanol (0.20 mL) was then added dropwise before removing the cooling bath and allowing the reaction to warm to ambient temperature for 1 h, the solution was transferred to a 28 mL vial containing H_2O (5 mL) and NH_4Cl (5 mL) (saturated aqueous solution of NH_4Cl) and the flask rinsed with Et_2O (15 mL). The vial was then sealed and shaken vigorously and the top layer carefully collected using a pipette and placed into another 28 mL vial. The aqueous layer was extracted twice more (7 ml of Et_2O) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. At this point a crude ^1H NMR and GC was taken to determine the presence and d.r. of product. The crude residue was then directly purified by flash column chromatography (SiO_2) to yield the desired cyclobutane.

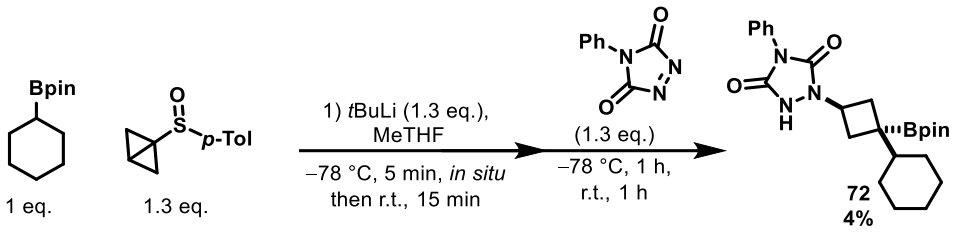
5.3. Electrophile Scope

2-(1-Cyclohexylcyclobutyl-3-*d*)-4,4,5,5-tetramethy-1,3,2-dioxaborolane (71)



According to **General Procedure A**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) reacted with deuterium oxide (0.20 mL, 37.0 eq., 8.90 mmol) to give a crude residue that was directly purified by flash column chromatography (SiO_2; 98:2 pentane:Et_2O) to afford the corresponding cyclobutane **71** (41 mg, 64 %) as a colourless oil. **TLC:** R_f = 0.28 (99:1 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.10 – 2.01 (m, 2H, CH_2), 1.82 – 1.59 (m, 7H, 3× CH_2, CHD), 1.36 – 0.86 (m, 7H, 3× CH_2, CH), 1.26 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 83.0 (O*C*(CH_3)$_2$), 48.3 (CH), 29.4 (CH(*C*H_2)$_2$), 29.2 (CH(*C*H_2)$_2$), 27.0 (CH_2), 24.9 (OC(*C*H_3)$_2$), 18.1 – 17.7 (t, J = 20.8 Hz, CHD) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{16}H_{28}BDO_2Na$ $[M+Na]^+$: 288.2219, found: 288.2222. **IR (thin film) ν_{max}:** 2976, 2923, 2851, 2190, 1462, 1448, 1382, 1297, 1197 and 1142 cm^{-1}

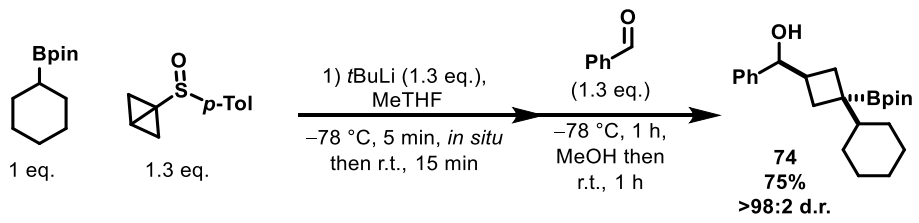
1-(3-cyclohexyl-3-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl) cyclobutyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (72)



According to **General Procedure A**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione (54 mg, 1.30 eq., 0.31 mmol) were coupled to give a crude residue (60:40 d.r. by crude NMR) that was directly purified by flash column chromatography (SiO_2; 10-50% EtOAc:pentane) to afford the corresponding cyclobutane **72** (8 mg, 4%, isolated as a single diastereoisomer) as a white solid. **TLC:** R_f = 0.50 (50:50 EtOAc:pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.63 (s, 1H, NH), 7.52 – 7.43 (m, 4H, 4× ArH), 7.38 – 7.33 (m, 1H, ArH), 4.64 – 4.55 (m, 1H, C*H*N), 2.48 – 2.43 (dt, J = 2.3, 8.6 Hz, 2H, (CH^aH^b)$_2$), 2.08 – 2.03 (dt, J = 2.3, 9.3 Hz, 2H, (CH^aH^b)$_2$), 1.70 – 1.60 (m, 7H, 3× CH_2, CH), 1.32 – 0.81 (m, 4H, 2× CH_2), 1.26 (s, 12H, Bpin) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{24}H_{34}BO_4N_3Na$ $[M+Na]^+$: 462.253893, found: 462.252756. **IR (thin film) ν_{max}:** 2976, 2924, 2851, 1771, 1695, 1503, 1422, 1388, 1313 and 1142 cm^{-1}

Insufficient material was isolated for ^{13}C NMR characterisation and melting point.

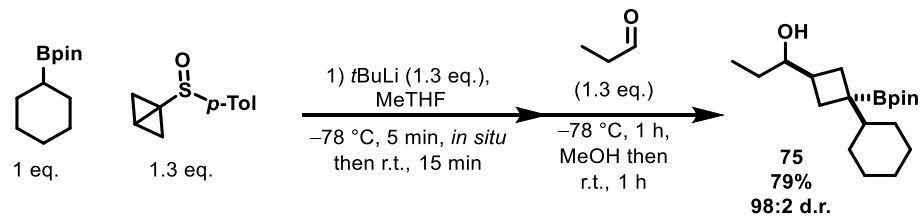
(3-Cyclohexyl-3-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)(phenyl)methanol (74)



According to **General Procedure B**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and benzaldehyde (0.03 mL, 1.30 eq., 0.31 mmol) were coupled to give a crude residue

(>98:2 d.r. by crude NMR) that was directly purified by flash column chromatography (SiO_2; 80:20 pentane:Et_2O) to afford the corresponding cyclobutane **74** (67 mg, 75 %, >98:2 d.r.) as a white solid. **m.p.:** 84 – 88 °C (pentane). **TLC:** R_f = 0.16 (80:20 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 – 7.16 (m, 5H, 5× ArH), 4.41 – 4.39 (dd, J = 7.5, 2.9 Hz, 1H, C*H*OH), 2.36 – 2.25 (m, 1H, C*H*(CH_2)$_2$), 2.21 – 2.15 (m, 1H, (C*H*^{a}H^b)^a), 1.93 – 1.87 (m, 1H, (C*H*^{a}H^b)^b), 1.71 – 1.48 (m, 8H, 3× CH_2, (CH^a*H*^{b})^a, (CH^a*H*^{b})^b), 1.22 – 0.79 (m, 5H, 2× CH_2, CH), 1.31 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (ArC), 128.4 (ArCH), 127.5 (ArCH), 126.2 (ArC), 83.1 (O*C*(CH_3)$_2$), 79.1 (CHOH), 49.2 (CH), 38.0 (*C*H(CH_2)$_2$), 32.6 (CH_2)^a, 32.3 (CH_2)^b, 29.1 (CH_2), 26.9 (CH_2), 26.9 (CH_2), 24.9 (OC(*C*H_3)$_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{23}H_{35}BO_3$ $[M+Na]^+$: 393.2576, found: 393.2579. **IR (thin film) ν_{max}:** 3407, 2976, 2955, 2845, 1451, 1385, 1308, 1297, 1234, 1188 and 1143 cm^{-1}

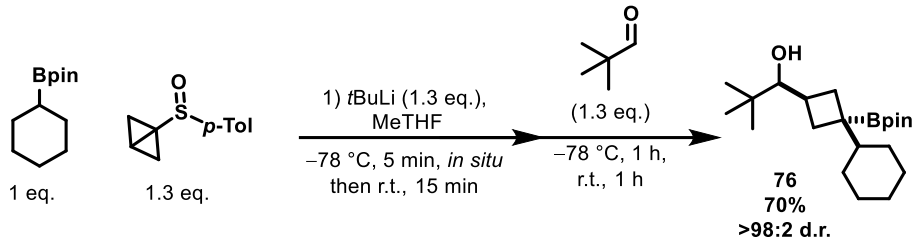
1-(3-Cyclohexyl-3-(3,3,4,4-tetramethylborolan-1-yl)cyclobutyl)propan-1-ol (75)



According to **General Procedure B**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and propanal (0.02 mL, 1.30 eq., 0.31 mmol) were coupled to give a crude residue (>98:2 d.r. by crude NMR) that was directly purified by flash column chromatography (SiO_2; 70:30 pentane:Et_2O) to afford the corresponding cyclobutane **75** (61 mg, 79 %, 98:2 d.r.) as a colourless oil that slowly solidifies to a white solid. **m.p.:** 80 – 82 °C (Et_2O). **TLC:** R_f = 0.26 (70:30 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.33 – 3.28 (m, 1H, C*H*OH), 2.21 – 2.15 (m, 1H, (C*H*^{a}H^b)^a), 2.13 – 2.07 (m, 2H, C*H*(CH_2)$_2$, (C*H*^{a}H^b)^b), 1.72 – 1.61 (m, 6H, 3× CH_2), 1.56 – 0.89 (m, 12H, CH_3, 4× CH_2, CH), 1.26 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 83.1 (O*C*(CH_3)$_2$), 78.0 (CHOH), 49.1 (CH), 36.7 (C*H*(CH_2)$_2$), 32.3 (CH_2)^a, 32.3 (CH_2)^b, 29.1 (CH_2),

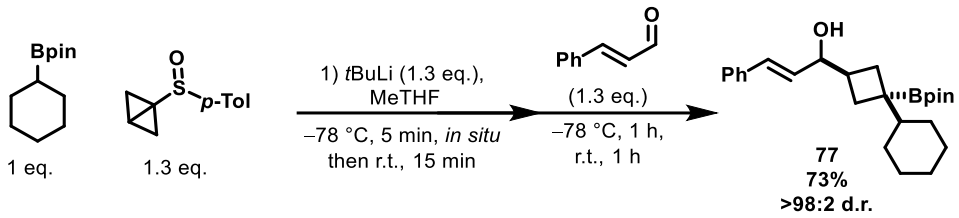
29.1 (CH_2), 27.64 (CH_2), 26.9 (CH_2), 26.9 (CH_2), 24.9 (OC(CH_3)$_2$), 10.2 (CH_3) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{19}H_{35}BO_3Na$ $[M+Na]^+$: 345.257497, found: 345.258383. **IR (thin film) ν_{max}:** 3367, 2975, 2922, 2850, 1449, 1385, 1233, 1191, 1143 and 1109 cm^{-1}

1-(3-Cyclohexyl-3-(3,3,4,4-tetramethylborolan-1-yl)cyclobutyl)-2,2-dimethylpropan-1-ol (76)



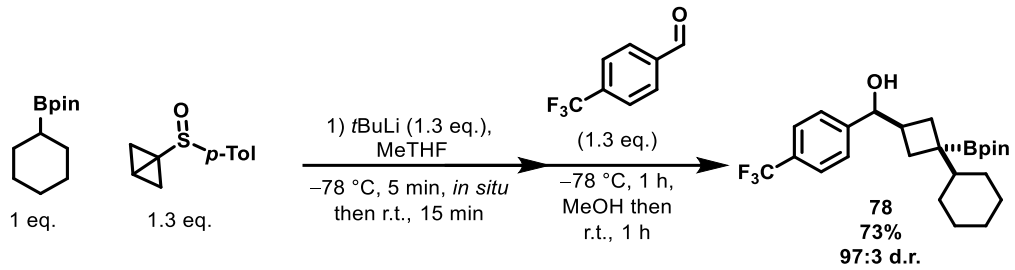
According to **General Procedure A**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and pivaldehyde (0.03 mL, 1.30 eq., 0.31 mmol) were coupled to give a crude residue that was directly purified by flash column chromatography (SiO_2; 80:20 pentane:Et_2O) to afford the corresponding cyclobutane **76** (59 mg, 70 %, >98:2 d.r.) as amorphous solid. **TLC:** R_f = 0.27 (80:20 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.06 – 3.04 (d, J = 7.1, 1H, (C*H*OH)), 2.30 – 2.10 (m, 3H, 2× (CH^aH^b)^a, (C*H*(CH^aH^b)), 1.71 – 1.55 (m, 8H, CH_2), 1.37 – 0.86 (m, 5H, CH_3, CH_2, CH), 1.26 (s, 12H, Bpin) 0.86 (s, 9H, (CCH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 83.5 (CH), 83.1 (O*C*(CH_3)$_2$), 49.2 (CH), 35.5 (CH_2), 35.4 (CH_2), 33.4 (CH_2), 33.2 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 26.9 (CH_2), 26.9 (CH_2), 26.3 (CH_3), 24.9, 24.9 (OC(*C*H_3)$_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{21}H_{39}BO_3Na$ $[M+Na]^+$: 373. 288831, found: 373.290374. **IR (thin film) ν_{max}:** 3448, 2975, 2922, 2850, 1449, 1385, 1297, 1234 and 1143 cm^{-1}

(*E*)-1-(3-Cyclohexyl-3-(3,3,4,4-tetramethylborolan-1-yl)cyclobutyl)-3-phenyl prop-2-en-1-ol (77)



According to **General Procedure B**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and cinnamaldehyde (0.04 mL, 1.30 eq., 0.31 mmol) were coupled to give a crude residue that was directly purified by flash column chromatography (SiO_2; 15-30% Et_2O:pentane) to afford the corresponding cyclobutane **77** (69 mg, 73 %, >98:2 d.r.) as a colourless oil. **TLC:** R_f = 0.13 (80:20 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.36 (m, 2H, ArH), 7.32 – 7.29 (m, 2H, ArH), 7.24 – 7.20 (m, 1H, ArH), 6.59 – 6.54 (d, J = 15.8 Hz , 1H, (C*H*CH)), 6.17 – 6.11 (dd, J = 6.5, 15.8 Hz, 1H, (CHC*H*)), 4.10 – 4.07 (t, J = 6.5 Hz, 1H, (C*H*OH)), 2.29 – 2.20 (m, 2H, C*H*$(CH_2)_2$, (C*H*^{a}H^b)^a), 2.15 – 2.09 (m, 1H, (C*H*^{a}H^b)^b), 1.73 – 1.55 (m, 8H, , (CH^a*H*^{b})^a, , (CH^a*H*^{b})^b, 3× CH_2), 1.29 – 0.80 (m, 5H, 2× CH_2, CH), 1.26 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.1 (Ar*C*CH), 130.5 (CH*C*H), 130.3 (ArC*C*H), 128.6 (ArH), 127.6 (ArH), 126.6 (ArH), 83.1 (O*C*$(CH_3)_2$), 77.5 (CHOH), 49.1 (CH), 36.7 (C*H*$(CH_2)_2$), 32.4 (CH_2), 31.9 (CH_2), 29.1 (CH_2), 26.9 (CH_2), 26.9 (CH_2), 24.9 (OC(*C*$H_3)_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{25}H_{37}BO_3Na$ $[M+Na]^+$: 419.273247, found: 419.273567. **IR (thin film) ν_{max}:** 3385, 2976, 2922, 2849, 1448, 1380, 1297, 1234 and 1142 cm^{-1}

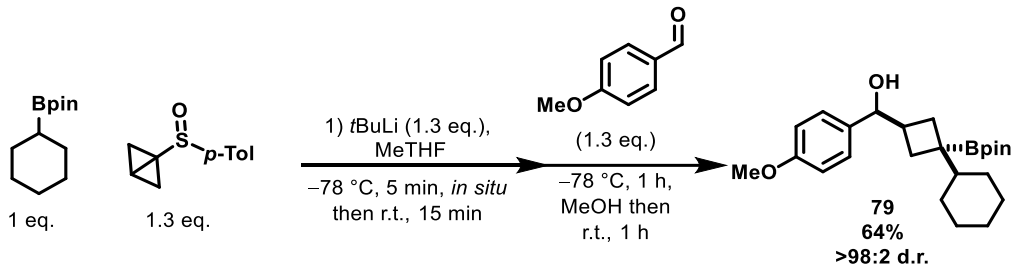
(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) cyclobutyl)(4-trifluoromethyl)(phenyl)methanol (78)



According to **General Procedure B**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.0 eq, 0.24 mmol) and 4-trifluoromethylbenzaldehyde (0.04 mL, 1.30 eq., 0.31 mmol) were coupled to give a crude residue (94:6 d.r. by crude NMR) that was directly purified by flash column chromatography (SiO_2; 10-20% Et_2O: pentane) to afford the corresponding cyclobutane **78** (74 mg, 70 %, 97:3 d.r.) as a colourless oil which slowly became a white solid over time. **m.p.:** 100 – 102 °C (pentane). **TLC:** R_f = 0.16 (80:20 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 7.56 (d, J = 8.2 Hz, 2H, ArH), 7.43 – 7.41 (d, J = 8.2 Hz, 2H, ArH), 4.54 – 4.52 (d, J = 7.3 Hz, 1H, C*H*OH), 2.39 – 2.27 (m, 1H, C*H*$(CH_2)_2$), 2.23 – 2.18 (m, 1H, (C*H*^{a}H^b)^a), 2.00 – 1.94 (m, 1H, (C*H*^{a}H^b)^b)), 1.73 – 1.55 (m, 8H, (CH^{a}C*H*^{b})^a, (CH^{a}C*H*^{b})^b, 3×CH_2), 1.29 – 0.80 (m, 5H, 2×CH_2, CH), 1.23 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.3 (Ar*C*CHOH), 130.1 – 129.1 (q, J = 32.4 Hz, *C*CF_3), 128.4 – 123.0 (q, J = 272.0 Hz, CF_3), 126.4 (ArCH), 125.4 – 125.3 (q, J = 3.7 Hz, C*C*H), 83.2 (O*C*$(CH_3)_2$), 78.2 (*C*HOH), 49.2 (CH), 38.2 (C*H*$(CH_2)_2$), 32.3 $(CH_2)^a$, 32.2 $(CH_2)^b$, 29.0 (CH_2), 26.9 (CH_2), 26.9 (CH_2), 24.9 (OC(*C*$H_3)_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{24}H_{34}BO_3F_3Na$ $[M+Na]^+$: 461.244965, found: 461.244887. **IR (thin film) ν_{max}:** 3386, 2977, 2924, 2851, 1620, 1385, 1324, 1124 and 1067 cm^{-1}

(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)

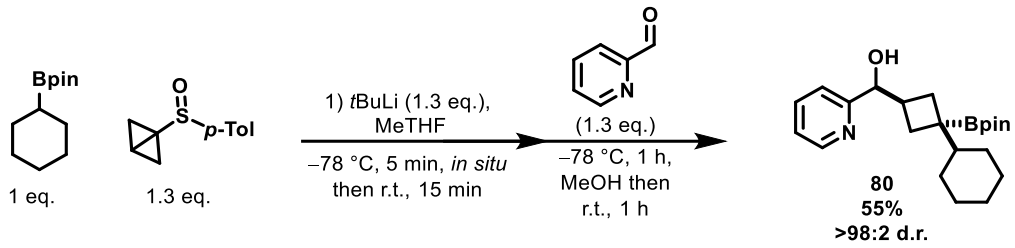
(4-mthoxyphenyl)methanol (79)



According to **General Procedure B**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and *p*-anisaldehyde (0.04 mL, 1.30 eq., 0.31 mmol) were coupled to give a crude residue (>98:2 d.r. by crude NMR) that was directly purified by flash column chromatography (SiO_2; 15-30% Et_2O:pentane) to afford the corresponding cyclobutane **79** (61 mg, 64 %, >98:2 d.r.) as a colourless oil. **TLC:** R_f = 0.10 (80:20 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 –7.21 (m, 2H, 2× ArH), 6.86 – 6.84 (m, 2H, 2× ArH), 4.42 – 4.40 (d, J = 7.5 Hz, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 2.41 – 2.24 (m, 2H, C*H*$(CH_2)_2$, (CH^aCH^b)^a), 1.98 – 1.93 (m, 1H, (CH^aCH^b)^b), 1.77 – 1.61 (m, 8H, (CH^{a}CH^b)^a, (CH^{a}CH^b)^b, 3× CH_2), 1.53 – 0.80 (m, 5H, 2×CH_2, CH), 1.23 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.1 (ArCOMe), 135.5 (Ar*C*CHOH), 127.5 (ArC), 113.8 (ArC), 83.1 (O*C*$(CH_3)_2$), 78.8 (CHOH), 55.4 (OCH_3), 49.2 (CH), 38.0 (C*H*$(CH_2)_2$), 32.8 $(CH_2)^a$, 32.3 $(CH_2)^b$, 29.1 (CH_2), 29.1 (CH_2), 26.9 (CH_2), 26.9 (CH_2), 24.9 (OC(*C*$H_3)_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{24}H_{37}BO_4Na$ $[M+Na]^+$: 423. 268146, found: 423.268410. **IR (thin film) ν_{max}:** 3432, 2976, 2922, 2849, 1611, 1511, 1381, 1297, 1244 and 1142 cm^{-1}

(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)

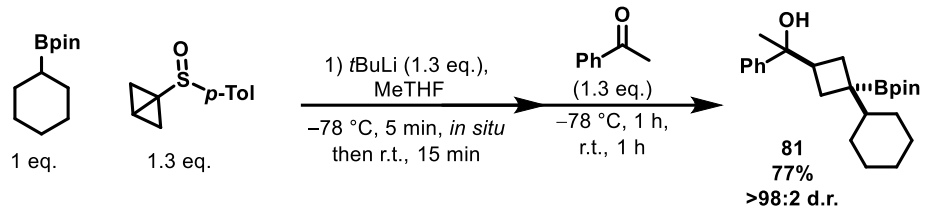
(pyridin-2-yl)methanol (80)



According to **General Procedure B**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and pincolinaldehyde (0.03 mL, 1.30 eq., 0.31 mmol) were coupled to give a crude residue (>98:2 d.r. by crude NMR) that was directly purified by flash column chromatography (SiO_2; 90:10 DCM:EtOAc) to afford the corresponding cyclobutane **80** (51 mg, 54%, >98:2 d.r.) as a viscous oil. **TLC:** R_f = 0.11 (90:10 DCM:EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 – 8.50 (m, 1H, ArH), 7.65 – 7.61 (m,1H, ArH), 7.20 – 7.15 (m, 2H, 2×ArH), 4.54 (d, J = 6.3 Hz, 1H, C*H*OH), 4.14 (broad s, 1H, OH), 2.41 – 2.31 (m, 1H, C*H*$(CH_2)_2$), 2.11 – 1.97 (m, 2H, C*H*^{a}H^b)^a, (C*H*^{a}H^b)^b), 1.83 – 1.62 (m, 8H, (CH^a*H*^{b})^a, (CH^a*H*^{b})^b, 3× CH_2), 1.31 – 0.81 (m, 5H, CH, 2× CH_2), 1.22 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0 (Ar*C*CHOH), 148.2 (ArC), 136.5 (ArC), 122.3 (ArC), 120.7 (ArC), 83.1 (O*C*$(CH_3)_2$), 75.9 (CHOH)), 49.0 (CH), 37.8 (C*H*$(CH_2)_2$), 32.1 $(CH_2)^a$, 31.1 $(CH_2)^b$, 29.8 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 26.9 (CH_2), 24.9 (OC(*C*$H_3)_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{22}H_{34}BO_3NNa$ $[M+Na]^+$: 394.2528, found: 394.2538. **IR (thin film) ν_{max}:** 3408, 2979, 2918, 2849, 1595, 1448, 1386, 1308 and 1143 cm^{-1}

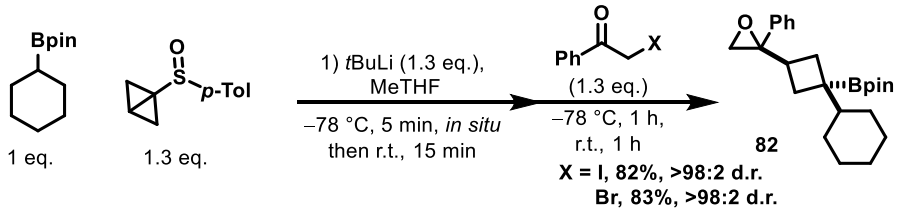
In the ^{1}H spectrum, the peak at δ 2.04 is grease. In the ^{13}C spectrum the peaks at δ 29.5, 22.8, 14.3 ppm are also grease.

1-(3-Cyclohexyl-3-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl) cyclobutyl)-1-phenethan-1-ol (81)



According to **General Procedure A**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and acetophenone (0.04 mL, 1.30 eq., 0.31 mmol) were coupled to give a crude residue (98:2 d.r. by crude NMR) that was directly purified by flash column chromatography (SiO_2; 90:10 pentane:Et_2O) to afford the corresponding cyclobutane **81** (70 mg, 76 %, 98:2 d.r.) as a colourless oil. **TLC:** R_f = 0.14 (90:10 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 2H, 2× ArH), 7.33 – 7.29 (m, 2H, 2× ArH), 7.23 – 7.19 (m, 1H, ArH), 2.54 – 2.45 (m, 1H, C*H*$(CH_2)_2$), 2.16 – 2.10 (m, 1H, (C*H*^{a}H^b)^a), 1.86 – 1.80 (m, 1H, (C*H*^{a}H^b)^b), 1.78 – 1.73 – 1.56 (m, 8H, (CH^a*H*^{b})^a,(CH^a*H*^{b})^b, 3× CH_2), 1.42 (s, 3H, CH_3) 1.35 – 0.93 (m, 4H, 2× CH_2, CH), 1.31 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.4 (ArC), 128.1(ArCH), 126.5 (ArCH), 125.1 (ArCH), 83.1 (O*C*$(CH_3)_2$), 74.3 (COHMe), 48.8 (CH), 41.7 (C*H*$(CH_2)_2$), 30.5 $(CH_2)^a$, 30.1 $(CH_2)^b$, 29.1 (CH_2), 29.0 (CH_2), 27.2 (CH_3), 26.9 (CH_2), 24.9 (OC(*C*$H_3)_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{24}H_{37}BO_3Na$ $[M+Na]^+$: 407.273231, found: 407.271470. **IR (thin film) ν_{max}:** 3485, 2975, 2922, 2850, 1446, 1386, 1307, 1233, 1196 and 1142 cm^{-1}

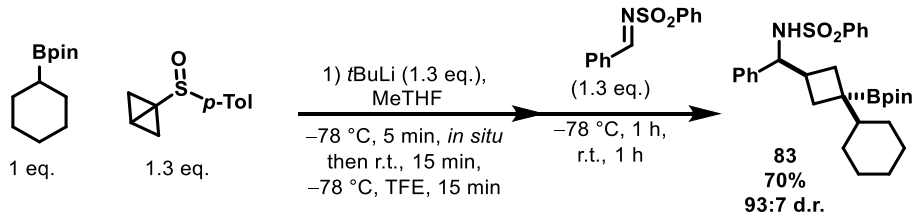
2-(1-Cyclohexyl-3-(2-phenyloxiran-2-yl)cyclobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (82)



According to **General Procedure A**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and iodoacetophenone (76 mg, 1.30 eq., 0.31 mmol) or bromoacetophenone (64 mg, 1.30 eq., 031 mmol) were coupled to give a crude residue (>98:2 d.r. by crude NMR) that was directly purified by flash column chromatography

(SiO_2; 95:5 pentane:Et_2O) to afford the corresponding cyclobutane **82** (75 mg, 82 %, >98:2 d.r. or 76 mg, 83%, >98:2 d.r.)as a white solid. **m.p.:** 85 – 89 °C (pentane). **TLC:** R_f = 0.16 (95:5 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 4H, 4× ArH), 7.19 – 7.15 (m, 1H, ArH), 2.91 (m, 1H, C*H*(CH_2)$_2$), 2.83 – 2.82 (d, *J* = 5.4 Hz, 1H, C*H*^{a}H^{b}O), 2.62 – 2.61 (d, *J* = 5.4 Hz, 1H, CH^a*H*^{b}O), 2.06 – 2.01 (m, 1H, (C*H*^{c}H^d)^a), 1.98 – 1.92 (m, 1H, (C*H*^{c}H^d)^b), 1.63 – 1.61 (m, 8H, 3× CH_2, (CH^c*H*^{d})^a and (CH^c*H*^{d})^b), 1.26 – 0.80 (m, 5H, CH, 2× CH_2) 1.19 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.1 (Ar*C*CO), 128.3 (ArCH), 127.4 (ArCH), 126.2 (ArCH), 83.1 (O*C*(CH_3)$_2$), 60.7 (ArC*C*O), 53.0 (CH_2O), 48.7 (CH), 33.1 (*C*H(CH_2)$_2$), 32.0 (CH_2)^a, 29.6 (CH_2)^b, 29.0 (CH_2), 28.9 (CH_2), 26.9 (CH_2), 26.9 (CH_2), 24.9 (CH_2), 24.9 (OC(*C*H_3)$_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{22}H_{34}BO_2$ [M+Na]$^+$: 405.2576, found: 405.2564. **IR (thin film) ν_{max}:** 2976, 2922, 2850, 1448, 1387, 1308, 1233, 1195, 1142 and 1109 cm^{-1}

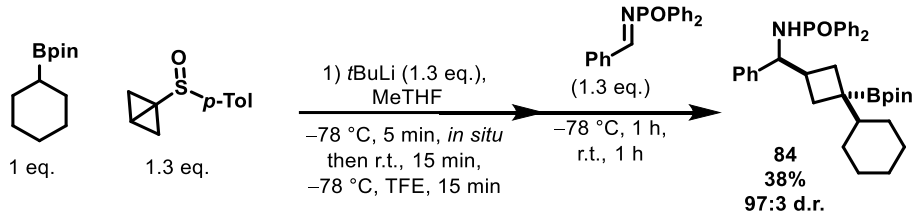
***N*-((3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl) cyclobutyl)(phenyl)methyl)benzenesulfonamide (83)**



According to a modified **General Procedure A**, after 15 min at ambient temperature, the reaction is cooled to –78 °C for 2 min before trifluoroethanol (0.20 mL) is added dropwise and left to stir for 15 min before the electrophile was added. Coupling cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and N-benzylidenebenezenesulfonamide (76 mg, 1.30 eq., 0.31 mmol) in the presence of trifluoroethanol to give a crude residue that was directly purified by flash column chromatography (SiO_2; 70:30 pentane: Et_2O) to afford the corresponding cyclobutane **83** (86 mg, 70 %, 93:7 d.r.) as a white solid. **m.p.:** 150 – 152 °C (DCM). **TLC:** R_f = 0.22 (60:40 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.53 (m, 2H, 2× ArH), 7.35 – 7.31 (m, 1H, ArH), 7.23 – 7.19 (m, 2H, 2× ArH), 7.04 – 7.01 (m, 3H, 2× ArH), 6.93 – 6.89 (m, 2H, 2× ArH), 4.79 (d, *J* = 7 Hz, 1H, NH), 4.04 – 4.00 (q, *J* = 7.0 Hz, 1H, C*H*NH). 2.25 – 2.09 (m, 2H, C*H*(CH_2)$_2$, (C*H*^{a}H^b)^a), 1.77 – 1.72

(m, 1H, (C*H*^{a}H^{b})^{b}), 1.62 – 0.73 (m, 13H, 5× CH_2, (CH^{a}*H*^{b})^{a}, (CH^{a}*H*^{b})^{b} and CH), 1.12 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.8 (ArC), 139.5 (ArC), 132.2 (ArCH), 128.7 (ArCH), 128.3 (ArCH), 127.3 (ArCH), 127.2 (ArCH), 126.9 (ArCH), 83.1 (O*C*(CH$_3$)$_2$) 64.1 (CHNH), 48.9 (CH), 36.8 (*C*H(CH$_2$)$_2$), 33.4 (CH$_2$)^{a}, 33.0 (CH$_2$), 28.9 (CH$_2$), 26.8 (CH$_2$), 26.8 (CH$_2$), 24.7 (CH$_2$), 24.7 (OC(*C*H$_3$)$_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{29}H_{40}BO_4NSNa$ $[M+Na]^+$: 532.266853, found: 532.265669. **IR (thin film) ν_{max}:** 3271, 2922, 1448, 1386, 1309, 1160, 1142 and 1092 cm^{-1}

_N_-((3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) cyclobutyl)(phenyl)methyl)-_P,P_-diphenylphosphinic amide (84)

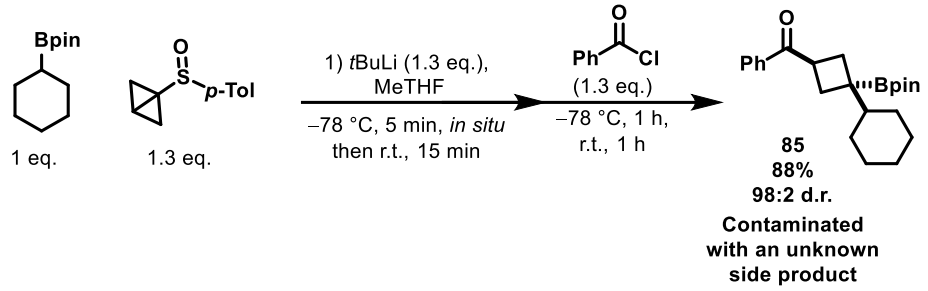


According to a modified **General Procedure A**, after 15 min at ambient temperature, the reaction is cooled to –78 °C for 2 min before trifluoroethanol (0.20 mL) is added dropwise and left to stir for 15 min before the electrophile was added. Coupling cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and *N*-benzylidene-*P,P*-diphenylphosphinic amide (95 mg, 1.30 eq., 0.31 mmol) in the presence of trifluoroethanol to give a crude residue that was directly purified by flash column chromatography (SiO_2; 60:10:30 Et_2O:acetone:pentane) to afford the corresponding cyclobutane **84** (62 mg, 38%, 97:3 d.r) as an amorphous white solid. **TLC:** R_f = 0.14 (60:10: 30 Et_2O:acetone:pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 2H, 2× ArH), 7.63 – 7.61 (m, 2H, 2× ArH), 7.43 – 7.33 (m, 4H, 4× ArH), 7.20 – 7.08 (m, 5H, 5× ArH), 7.02 – 7.00 (m, 2H, ArH), 3.93 – 3.93 – 3.87 (q, J = 8.8 Hz, 1H, C*H*NH), 3.08 – 3.04 (t, J = 6.80 Hz, 1H, NH), 2.34 – 2.22 (m, 2H, C*H*(CH$_2$)$_2$, (C*H*^{a}H^{b})^{a}), 1.77 – 1.61 (m, 1H, (C*H*^{a}H^{b})^{b}), 1.61 – 0.75 (m, 13H 5× CH$_2$, (CH^{a}*H*^{b})^{a}, (CH^{a}*H*^{b})^{b}, CH), 1.14 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 83.0 (O*C*(CH$_3$)$_2$), 61.2 (CHNH), 49.1 (CH), 38.6 *C*H(CH$_2$)$_2$), 33.9 (CH)^{a}, 33.2 (CH$_2$)^{b}, 29.0 (CH$_2$), 29.0 (CH$_2$), 26.9 (CH$_2$), 26.9 (CH$_2$), 24.9 (CH$_2$), 24.9 (OC(*C*H$_3$)$_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{35}H_{45}BNO_3Na$ $[M+Na]^+$: 592.3128, found: 592.3126. **IR**

(thin film) ν_{max}**:** 3198, 3059, 2976, 2923, 2850, 1438, 1385, 1307, 1297, 1189 and 1142 cm^{-1}

Peaks in the ^{13}C NMR in the region of δ142.7 – 128.7 ppm could not be assigned due to ^{31}P coupling.

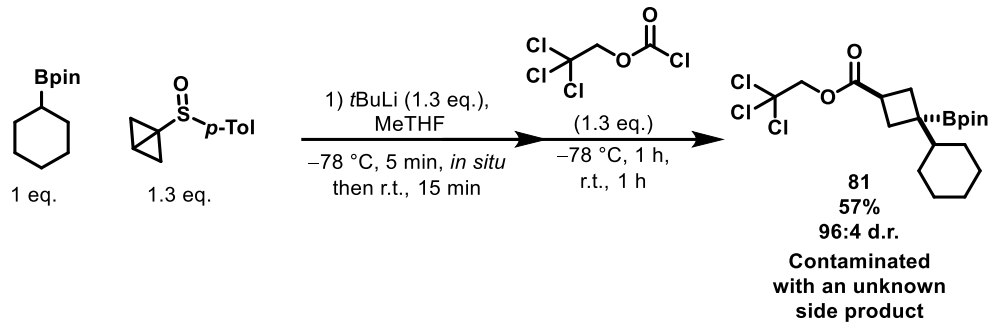
(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) cyclobutyl)(phenyl)methanone (85)



According to **General Procedure A**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and benzoyl chloride (0.04 mL, 1.30 eq., 0.31 mmol) were coupled to give a crude residue that was directly purified by flash column chromatography (SiO_2; 95:5 pentane:Et_2O) to afford the corresponding cyclobutane **85** (77 mg, 88 %, 98:2 d.r.) as a white solid which contains an unknown side product. **TLC:** R_f = 0.13 (95:5 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) 3.82 – 3.72 (quintet, *J* = 8.8 Hz, 1H, ArCOC*H*), 2.44 – 2.39 (dt, *J* = 2.2, 8.9 Hz, 2H, CH(CH_2)[a]), 2.17 – 2.11 (dt, *J* = 2.2, 9.7 Hz, 2H, CH(CH_2)[b]), 1.79 – 1.62 (m, 4H, 2× CH_2), 1.50 – 0.90 (m, 6H, 2× CH_2, 2×CH), 1.31 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* 201.4 (PhCO), 132.9 (ArC), 130.3 (ArC), 128.6 (ArC), 128.5 (ArC), 83.3 (O*C*(CH_3)$_2$), 48.3 (CH), 38.2 (CH), 32.7 CH(*C*H_2)$_2$, 28.8 (CH_2), 26.8 (CH_2), 26.8 (CH_2), 24.9 (OC(*C*H_3)$_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{23}H_{34}BO_3$ $[M+H]^+$: 369.259969, found: 369.260699. **IR (thin film)** ν_{max}**:** 2976, 2923, 2849, 1790, 1730, 1679, 1598, 1581, 1449, 1358, 1310, 1213 and 1141 cm^{-1}

Hydrogen atoms in the range of *δ* 8.17 – 7.41 can not be confidently assigned due to the presence of an unknown impurity.

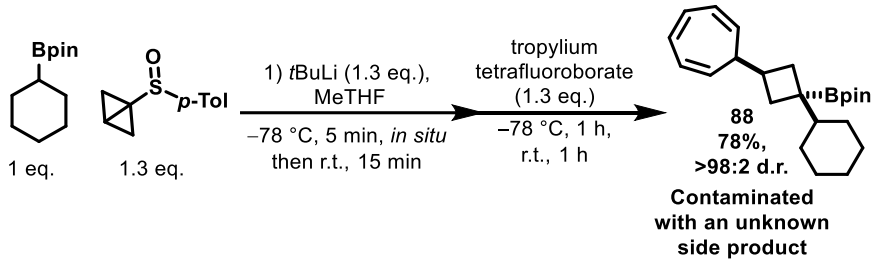
2,2,2-Trichloroethyl 3-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) cyclobutane-1-carboxylate (85)



According to **General Procedure A**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and 2,2,2-Trichloroethoxycarbonyl chloride (0.04 mL, 1.30 eq., 0.31 mmol) were coupled to give a crude residue that was directly purified by flash column chromatography (SiO_2; 5-20% Et_2O:pentane) to afford the corresponding cyclobutane **85** (60 mg, 57 %, 96:4 d.r.) as a colourless oil. **TLC:** R_f = 0.18 (95:5 Et_2O:pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.72 (s, 2H, CH_2OCO), 3.12 – 3.03 (m, 1H, CHCO$_2$), 2.40 – 2.35 (m, 2H, (CH^aH^b)$_2$), 2.10 – 2.04 (m, 2H, (CH$^aH^b$)$_2$), 1.73 – 1.58 (m, 7H, CH, 3× CH_2), 1.34 – 0.79 (m, 4H, 2× CH_2), 1.27 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.9 (OCO), 83.4 (OC(CH$_3$)$_2$), 73.9 (CCl_3), 48.4 (CH), 33.7 (CH), 32.6 (CH_2), 28.7 (CH_2), 26.8 (CH_2), 26.8 (CH_2), 25.0 (OC(CH$_3$)$_2$), 24.9 (OC(CH$_3$)$_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{19}H_{30}BO_4Cl_3Na$ $[M+Na]^+$: 461.119843, found: 461.120579. **IR (thin film) ν_{max}:** 2977, 2924, 2851, 1750, 1449, 1372, 1311, 1232, 1139, 1232 and 1139 cm^{-1}

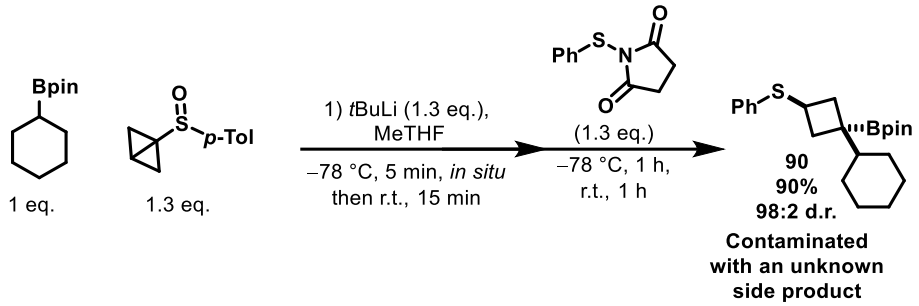
A singlet in the ^{1}H NMR at 4.85 ppm is an unknown impurity.

2-(3-(Cyclohepta-2,4,6-trien-1-yl)-1-cyclohexylcyclobutyl)-4,4,5,5,-tetra methyl-1,3,2-dioxaborolane (88)



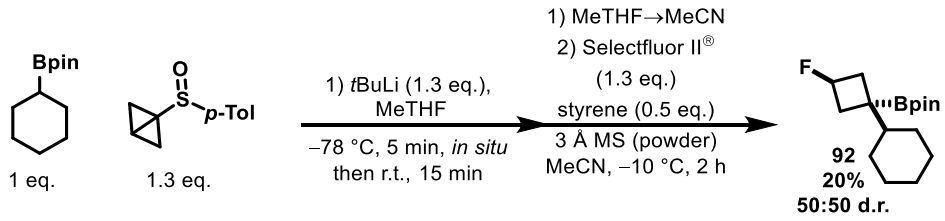
According to **General Procedure A**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) and tropylium tetrafluoroborate (55 mg, 1.30 eq., 0.31 mmol) were coupled to give a crude residue that was directly purified by flash column chromatography (SiO_2; 1:99 Et_2O:pentane) to afford the corresponding cyclobutane **88** (62 mg, 78 %, >98:2 d.r.) as a white solid. **TLC:** R_f = 0.25 (1:99 Et_2O:pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.63 – 6.61 (t, J = 3.5 Hz, 2H, 2× C*H*=CH), 6.18 – 6.14 (m, 2H, 2× C*H*=CH), 5.19 – 5.08 (m, 2H, 2× C*H*=CH), 2.45 – 2.32 (m, 3H, C*H*(CH_2)$_2$, (C*H*^{a}H^b)$_2$), 1.76 – 1.63 (m, 6H, 3× CH_2), 1.50 – 1.43 (m, 2H, (CH^a*H*^{b})$_2$, 1.34 – 0.87 (m, 6H, 2× CH, 2× CH_2), 1.29 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.9 (*C*H=CH), 25.7 (CH=*C*H), 125.1 (*C*H=CH), 83.1 (O*C*(CH_3)$_2$), 49.1 (CH), 46.0 (CH), 34.1 (CH_2), 33.7 (*C*H(CH_2)$_2$), 29.2 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 24.9 (OC(*C*H_3)$_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{22}H_{35}BO_2Na$ $[M+Na]^+$: 377.2626, found: 377.2622. **IR (thin film) ν_{max}:** 2921, 2849, 1380, 1310, 1140, 859, 744, 704 and 675 cm^{-1}

2-(1-Cyclohexyl-3-(phenylthio)cyclobutyl)-4,4,5,5,-tetramethyl-1,3,2-dioxaborolane (90)



According to **General Procedure A**, cyclohexyl pinacol boronic ester **24** (50 mg, 1.00 eq, 0.24 mmol) reacted with 1-(phenylthio)pyrrolidine-2,5-dione (64 mg, 1.30 eq., 0.31 mmol) to give a crude residue that was directly purified by flash column chromatography (SiO_2; 50:50 pentane:PhMe) to afford the corresponding cyclobutane **90** (57 mg, 61%, >98:2 d.r.) as a white solid. **m.p.:** 80 – 84 °C (pentane). **TLC:** R_f = 0.39 (50:50 pentane:toluene). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.15 (m, 4H, 4× ArH), 7.11 – 7.04 (m, 1H, ArH), 3.75 – 3.64 (m, 1H, C*H*$(CH_2)_2$), 2.57 – 2.52 (m, 2H, (C*H*^{a}H^b)$_2$) 1.81 – 1.76 (m, 2H, (CH^a*H*^{b})$_2$), 1.64 – 1.52 (m, 6H, 3× CH_2), 1.29 – 0.80 (m, 5H, 2× CH_2, CH), 1.19 (s, 12H, Bpin) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.3 (ArCS), 129.1(ArCH), 128.9 (ArCH), 125.7 (ArCH), 83.4 (O*C*$(CH_3)_2$), 49.0 (CH), 38.6 (CH_2), 36.1 (*C*H$(CH_2)_2$), 29.0 (CH_2), 26.8 (CH_2), 26.8 (CH_2), 24.9 (OC(*C*$H_3)_2$) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{22}H_{33}BO_2SNa$ $[M+Na]^+$: 395.2191, found: 395.2191. **IR (thin film) ν_{max}:** 2978, 2922, 2850, 1585, 1480, 1449, 1384, 1310, 1235, 1187 and 1141 cm^{-1}

2-(1-cyclohexyl-3-fluorocyclobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (92)



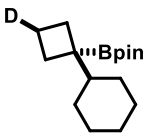
According to a modified literature procedure[53], *tert*-Butyl lithium (in pentane, 0.31 mmol, 1.30 eq.) was added dropwise to a solution of MeTHF (2.1 mL), bicyclobutyl sulfoxide **57** (60 mg, 0.31 mmol, 1.30 eq.) and cyclohexyl pinacol boronic ester **24** (50 mg, 0.24 mmol, 1.00 eq.) at –78 °C (dry ice/acetone) and allowed to stir for 5 min. After removing the cool bath, the reaction was

allowed to warm to ambient temperature for 15 min before being cooled 0 °C and concentrated under reduced pressure. A nitrogen atmosphere was re-established and MeCN (2.1 mL) was added. In a separate flask, styrene (14 μL, 0.12 mmol, 0.50 eq) was added to a prepared suspension of Selectfluor® II (99 mg, 0.31 mmol, 1.30 eq.) and 3 Å molecular sieves (powder 100 mg) in MeCN (2.1 mL) under a nitrogen atmosphere at –10 °C. After 10 mins, the prepared boronate complex solution was added dropwise by a syringe at –10 °C and stirred for 2 h before being transferred to a 28 mL vial containing 5 mL of H_2O and NH_4Cl (saturated solution) and the flask rinsed with 15 mL of Et_2O. The vial was then sealed and shaken vigorously and the top layer carefully collected using a pipette and placed into another 28 mL vial. The aqueous layer was extracted twice more (7 ml of Et_2O) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was directly purified by flash column chromatography (SiO_2; 98:2 pentane:Et_2O) to afford the corresponding cyclobutane **92** (13 mg, 20 %, 50:50 d.r.) as a colourless oil. **TLC:** R_f = 0.14 (98:2 pentane:Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.94 – 4.86 (q, J = 7.3 Hz, 1H, $(CHF)^a$), 4.80 – 4.72 (q, J = 7.2 Hz, 1H, $(CHF)^b$), 2.52 – 2.46 (m, 4H, $(CH_2)^a$, $(CH_2)^b$), 1.93 – 1.56 (m, 14H, $(CH_2)^a$, $(CH_2)^b$, 2× CH, 4× CH_2), 1.32 – 0.84 (m, 12H, 6× CH_2), 1.23 (s, 24H, Bpin) ppm. **HRMS (*m/z*):** (ESI) calc'd for $C_{16}H_{28}BO_2FNa$ $[M+Na]^+$: 305.2062, found: 305.2059. **IR (thin film) ν_{max}:** 2978, 2924, 2851, 1149, 1385, 1311, 1236 and 1142 cm^{-1}

The product was isolated with an unknown side product which is observed in the ^{1}H NMR spectrum with peaks at δ 5.26 – 5.23, 5.11 – 5.08 and 2.83 – 2.76 ppm.

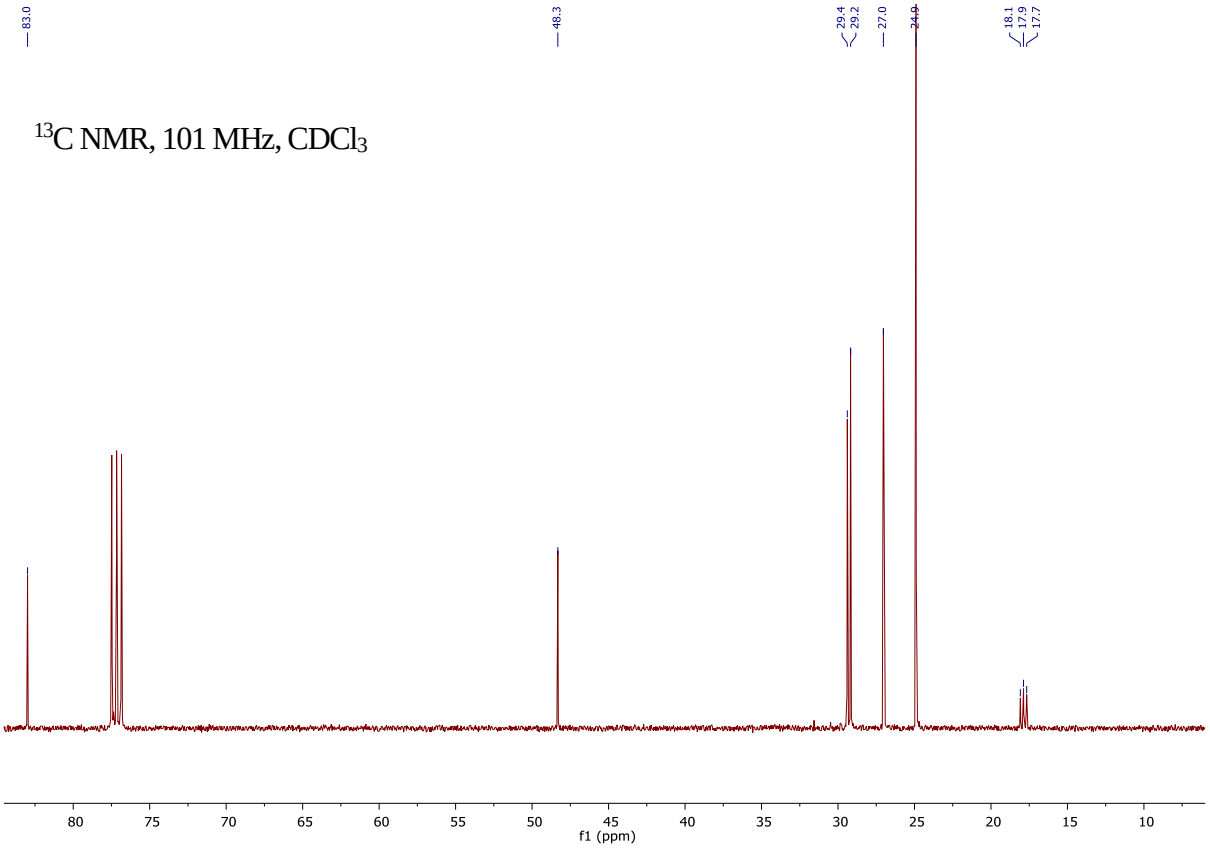
6. Appendix

6.1. Spectra of Compounds

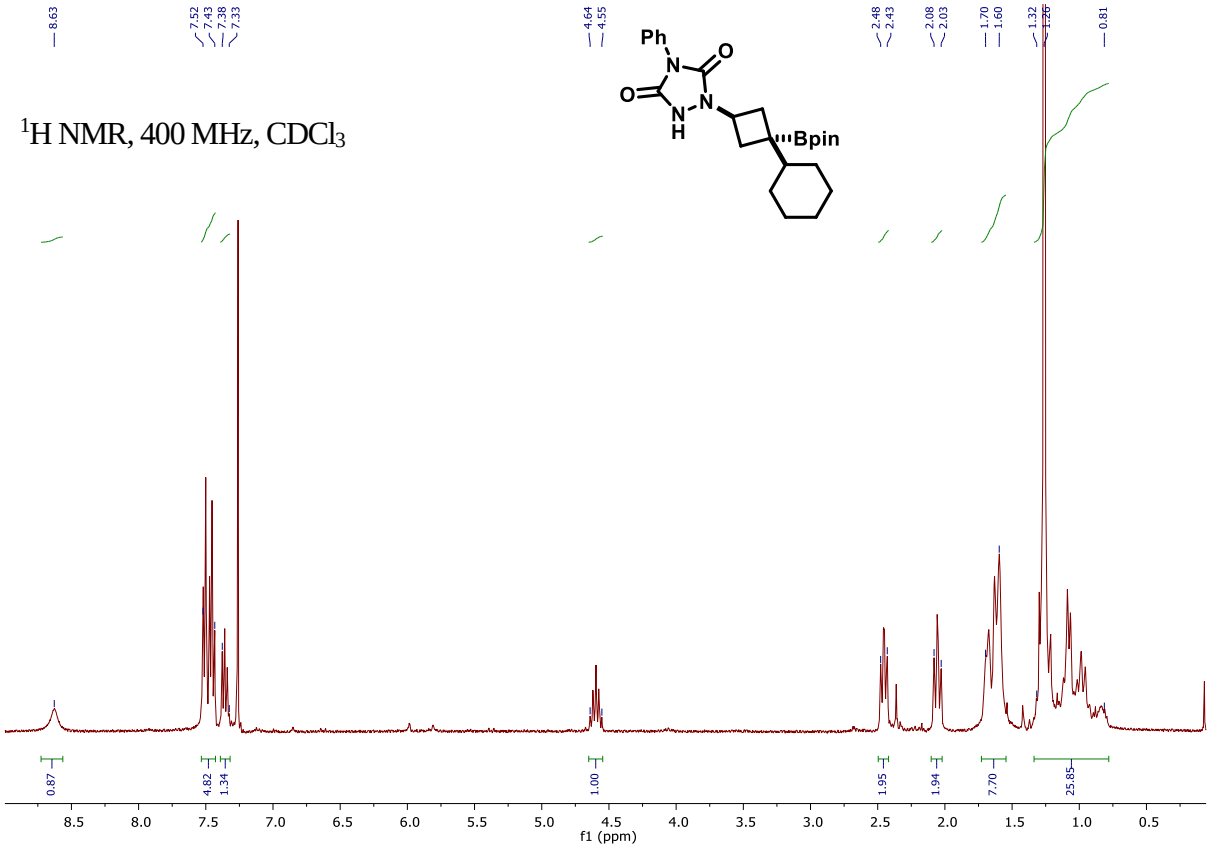


^{1}H NMR, 400 MHz, $CDCl_3$

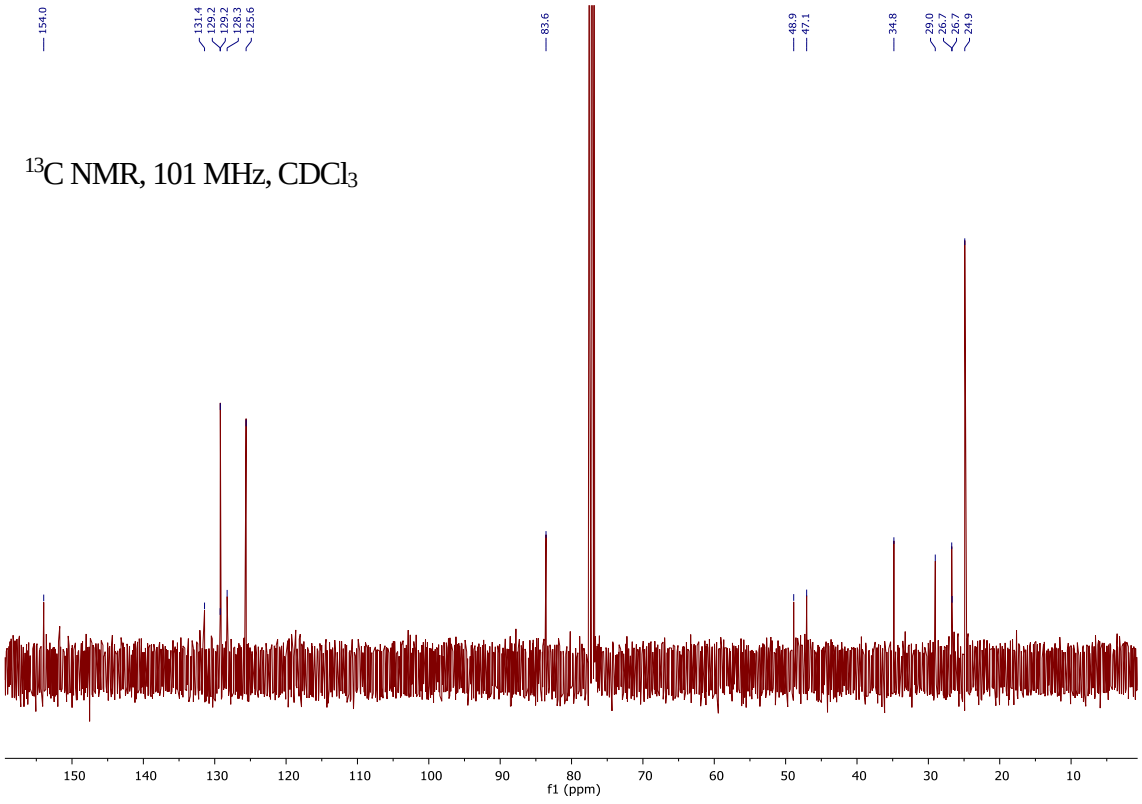
^{13}C NMR, 101 MHz, $CDCl_3$



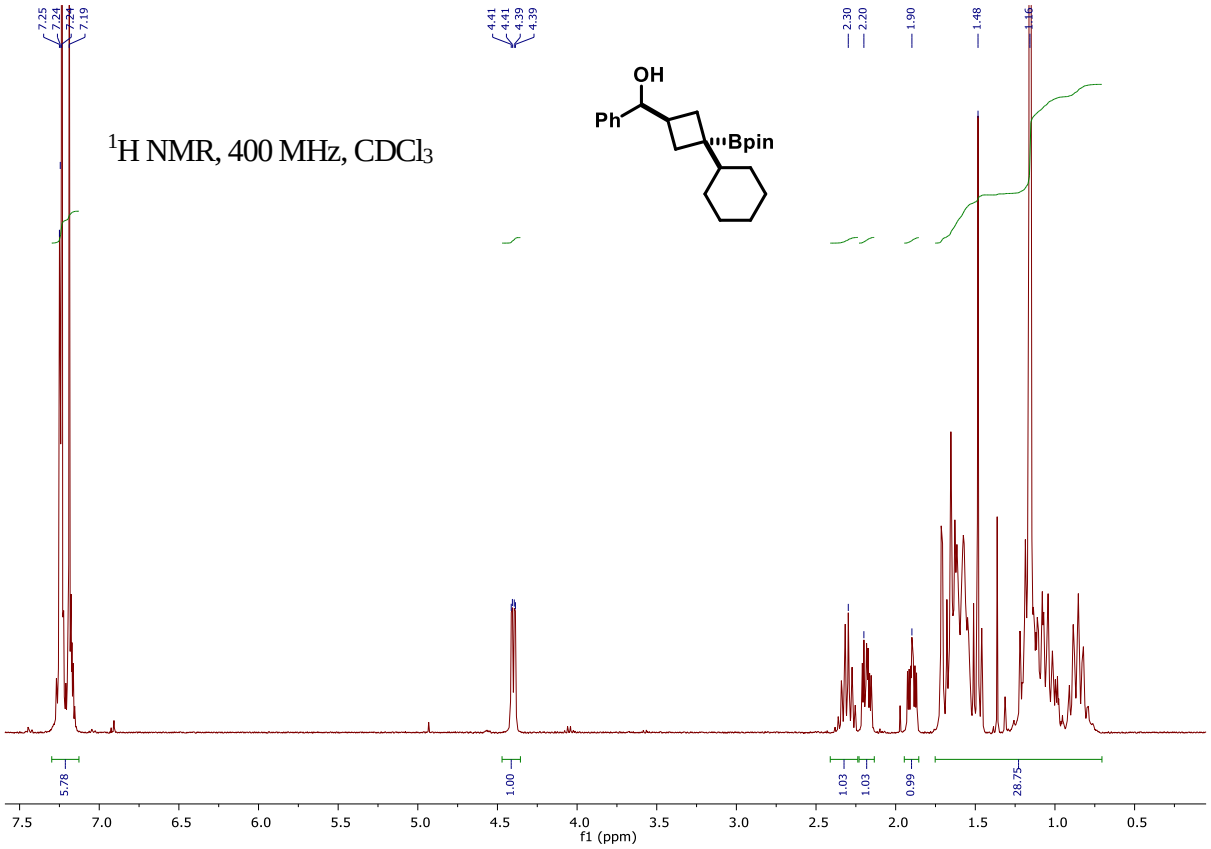
^{1}H NMR, 400 MHz, $CDCl_3$



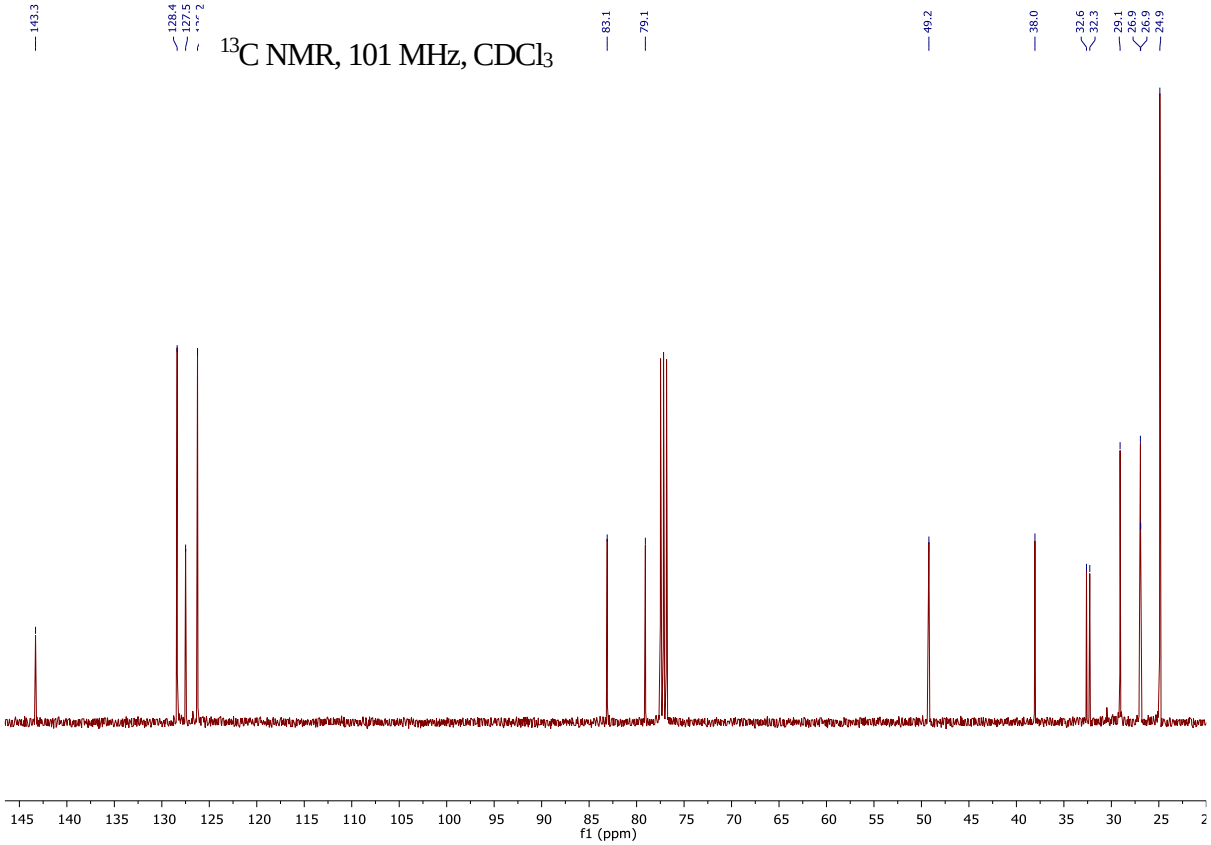
^{13}C NMR, 101 MHz, $CDCl_3$



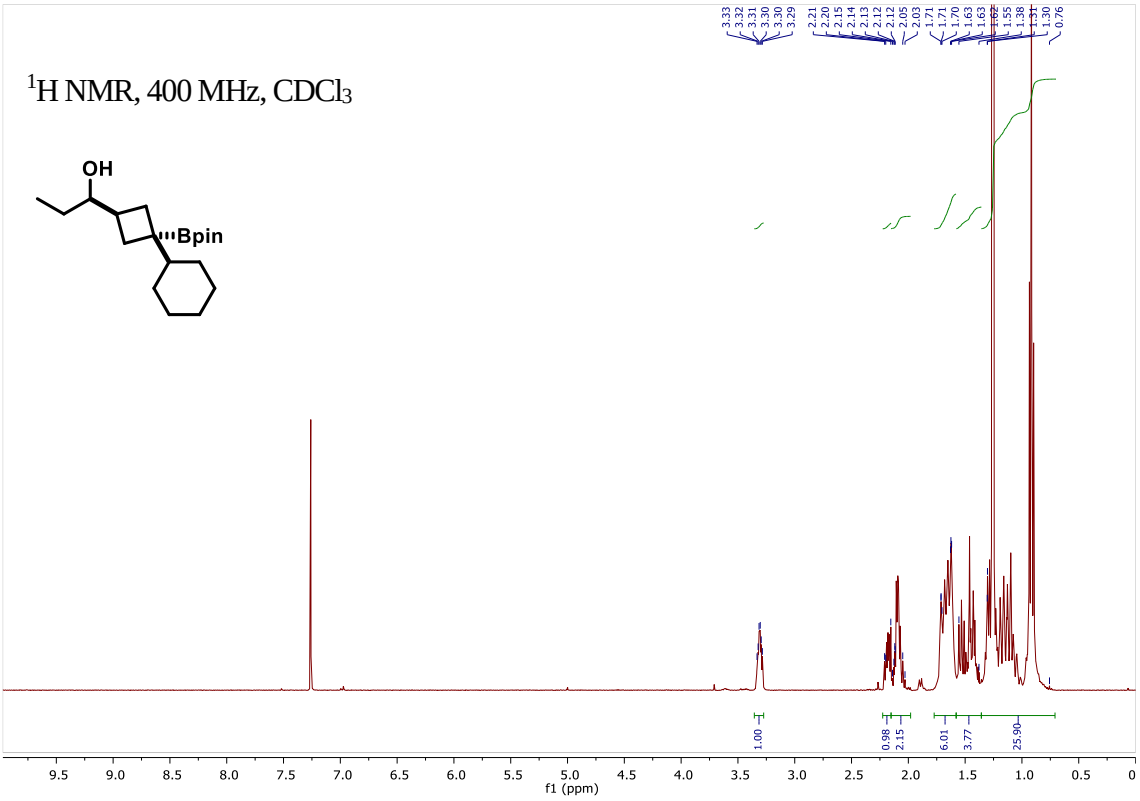
^{1}H NMR, 400 MHz, $CDCl_3$



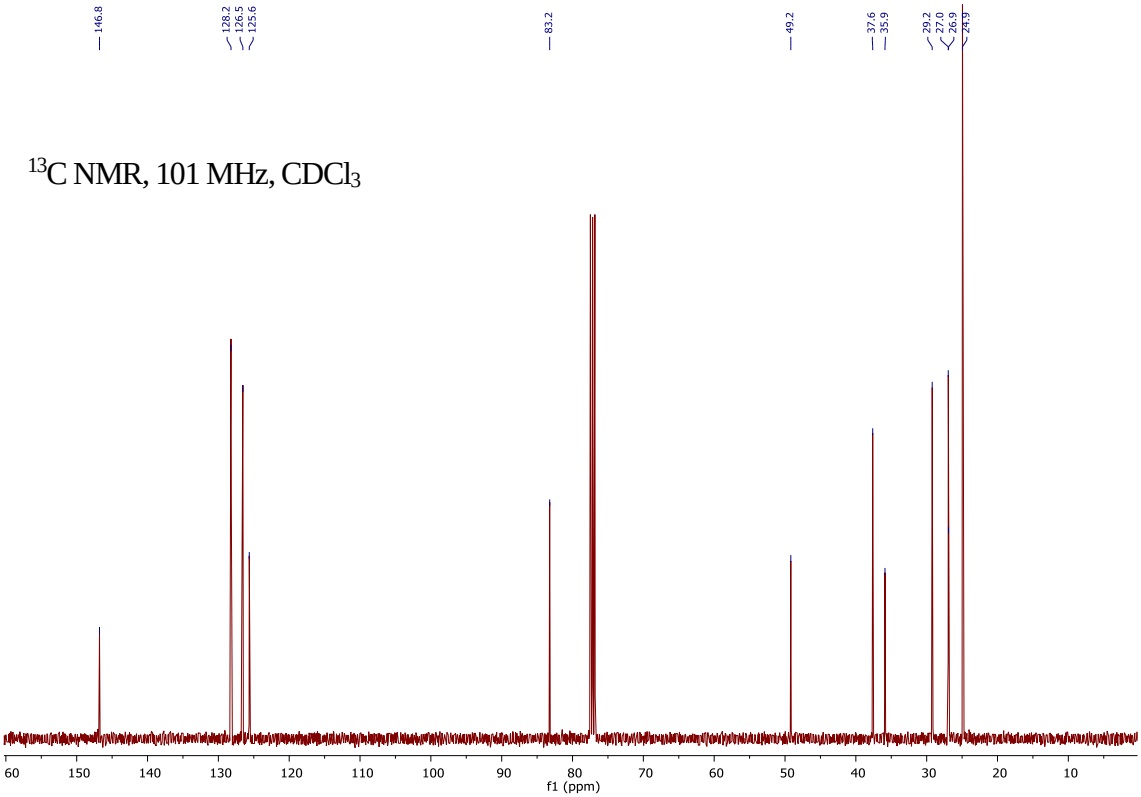
^{13}C NMR, 101 MHz, $CDCl_3$



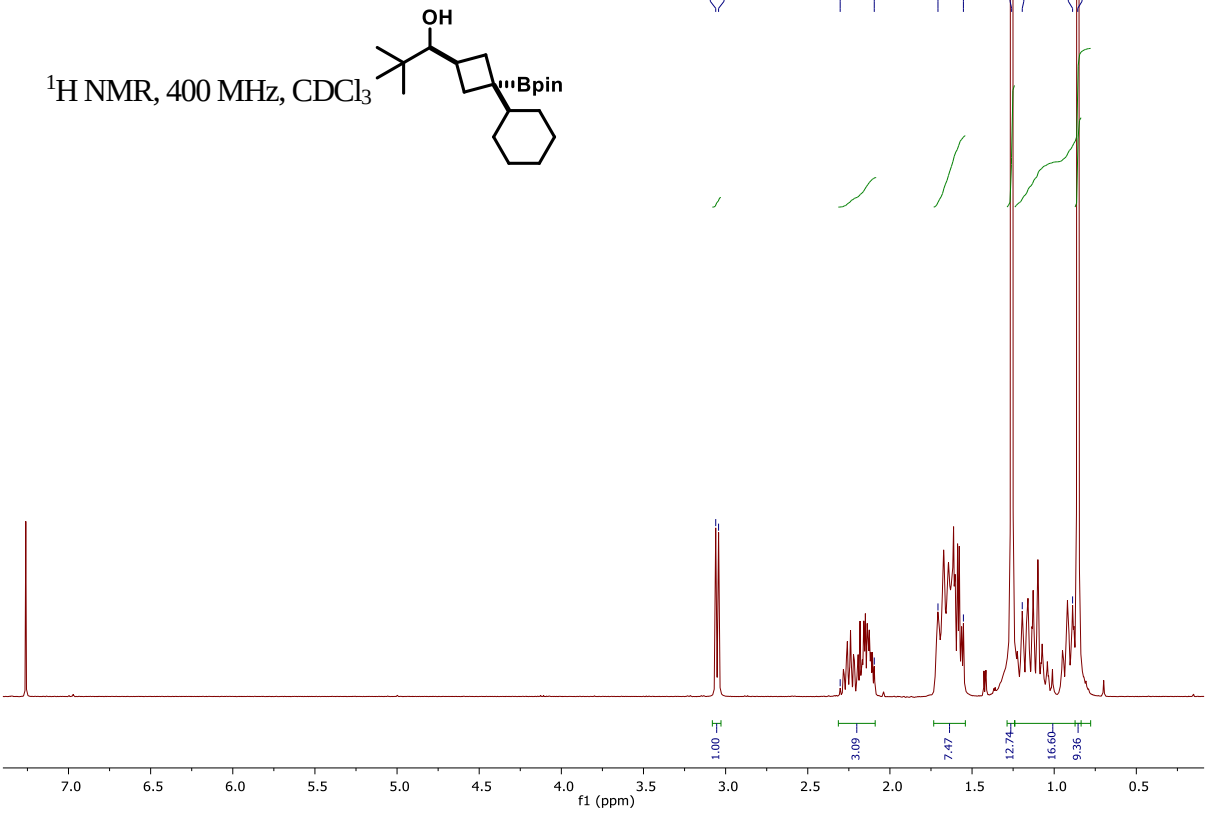
^{1}H NMR, 400 MHz, $CDCl_3$



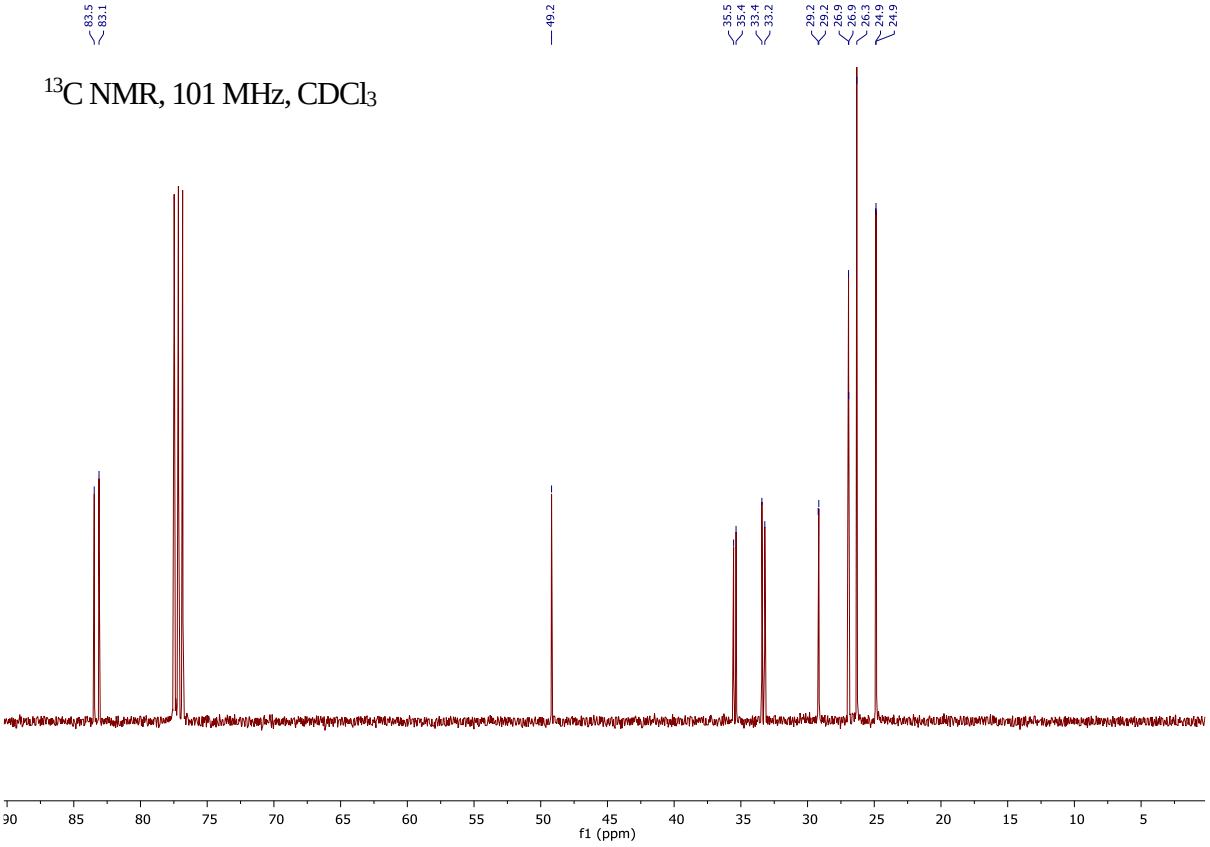
^{13}C NMR, 101 MHz, $CDCl_3$



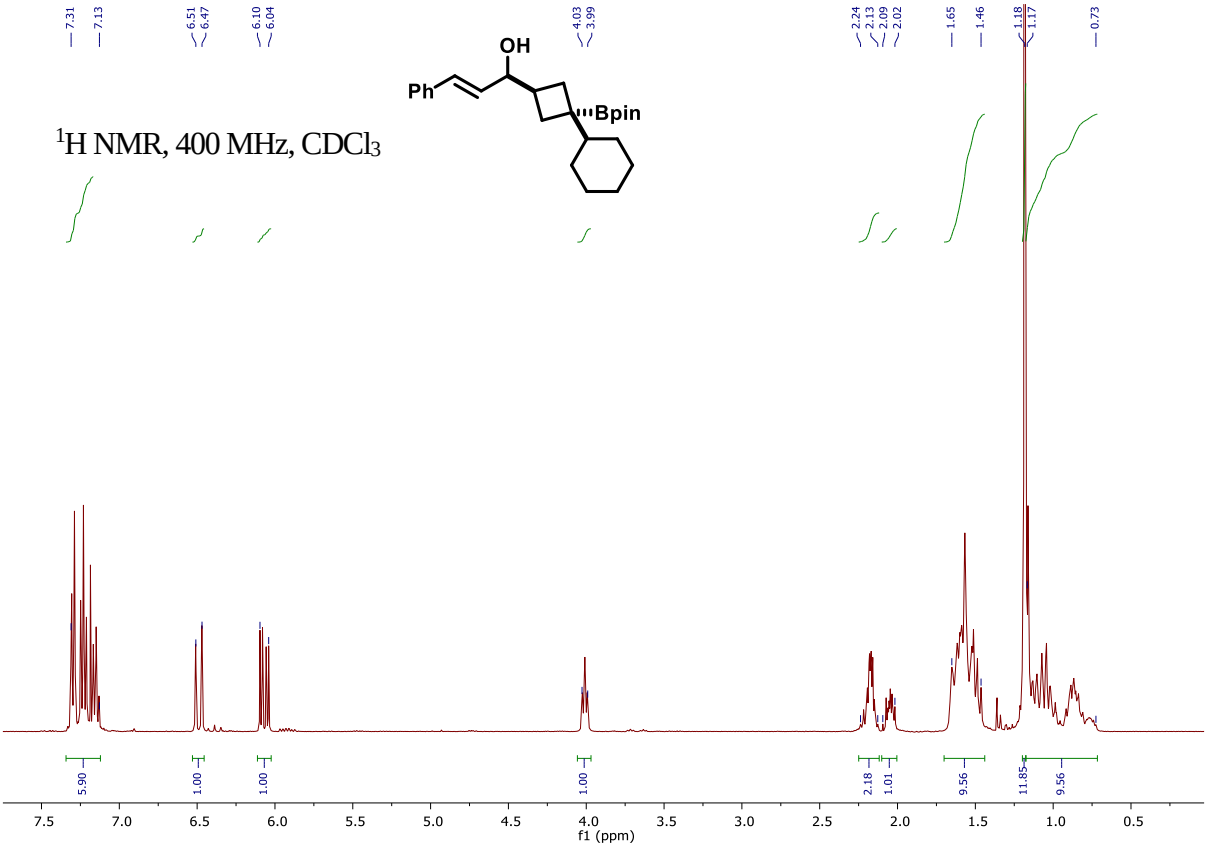
^{1}H NMR, 400 MHz, $CDCl_3$



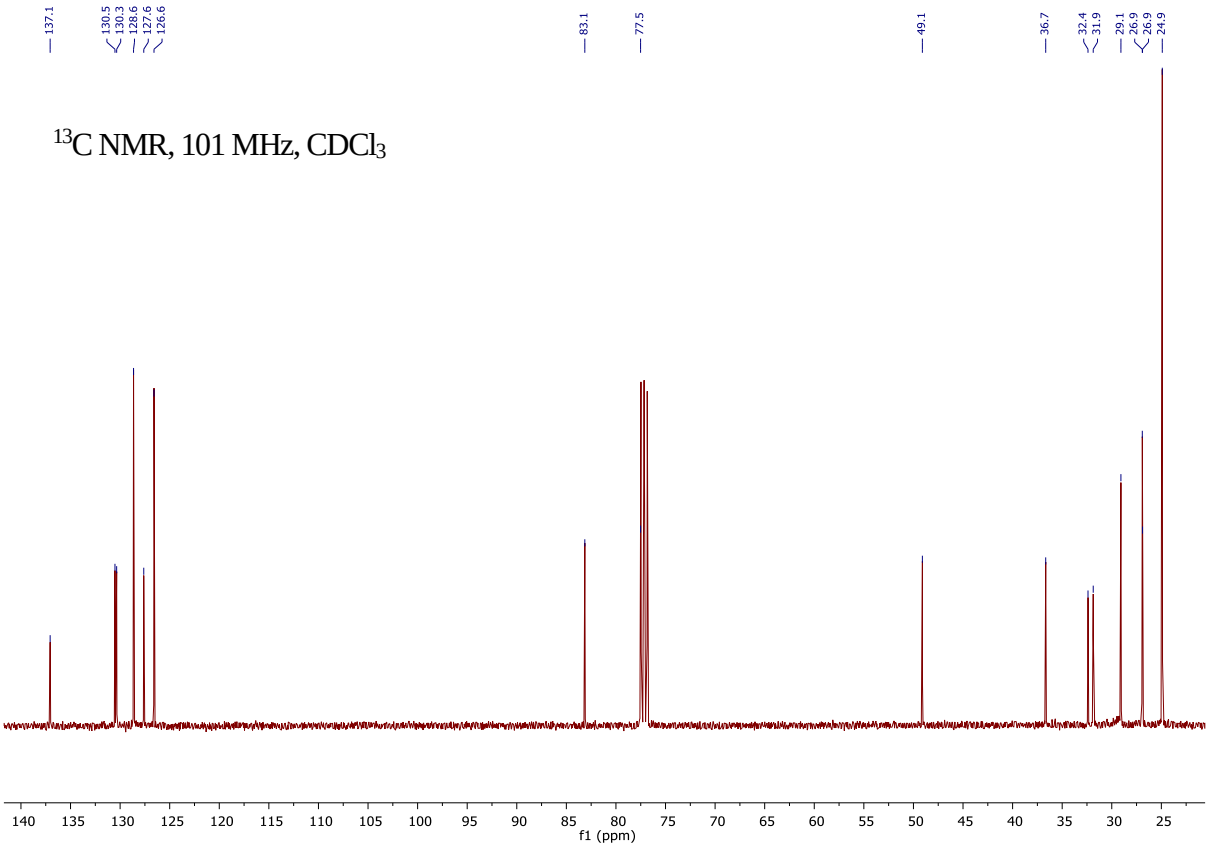
^{13}C NMR, 101 MHz, $CDCl_3$



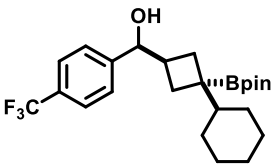
^{1}H NMR, 400 MHz, $CDCl_3$



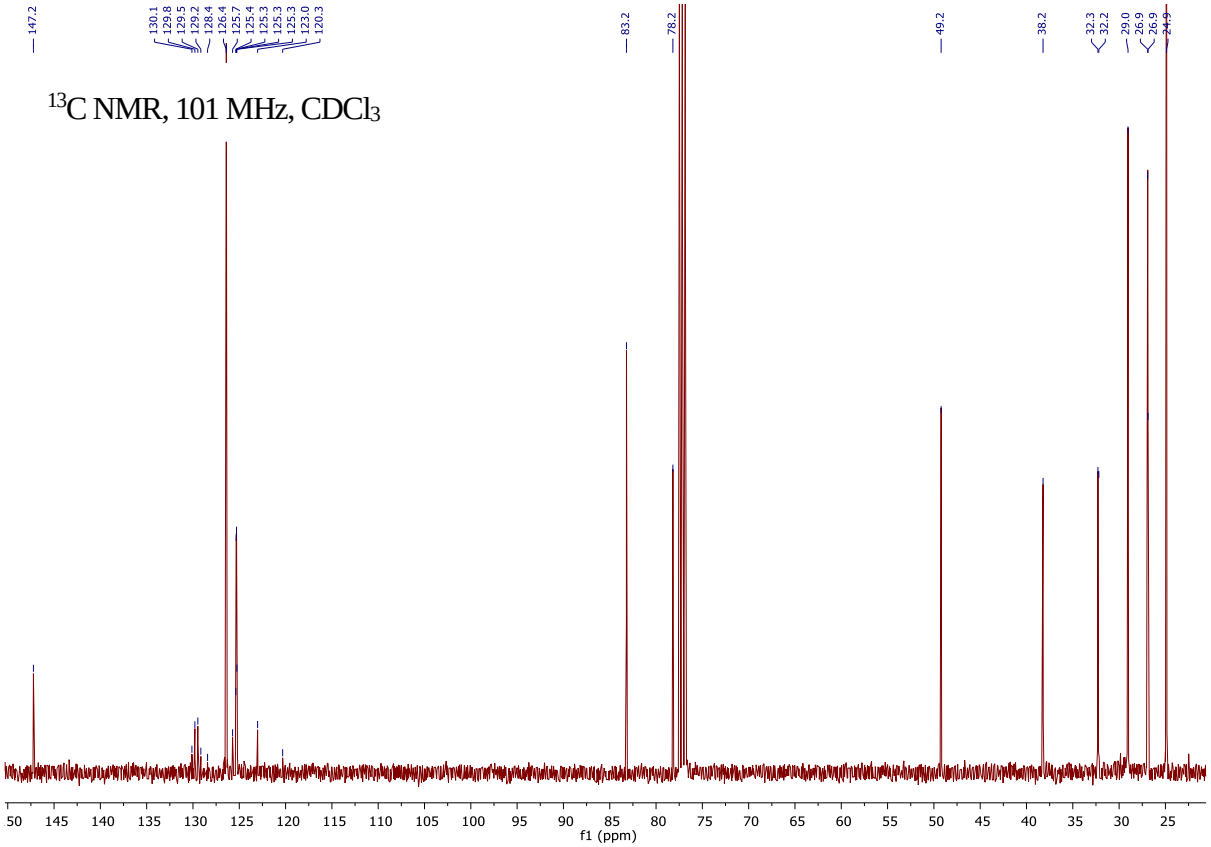
^{13}C NMR, 101 MHz, $CDCl_3$



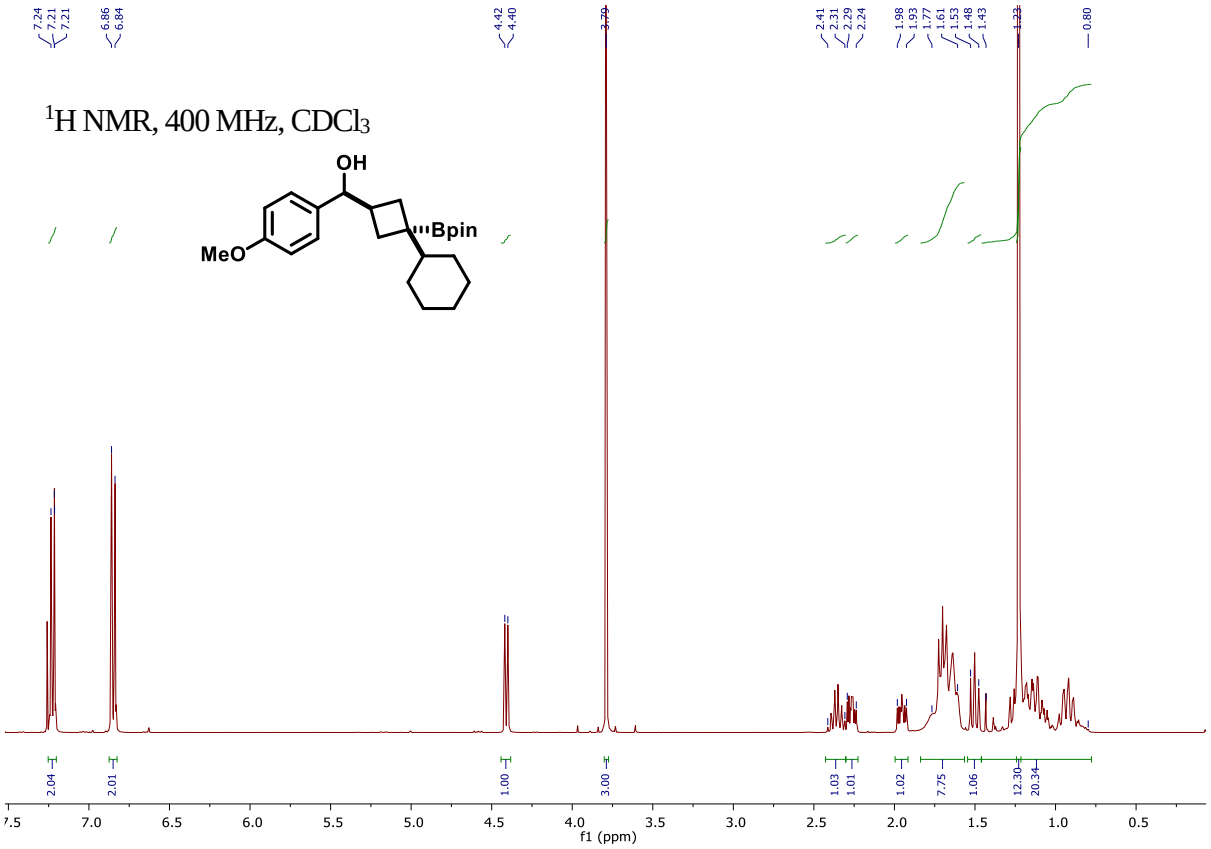
^{1}H NMR, 400 MHz, $CDCl_3$



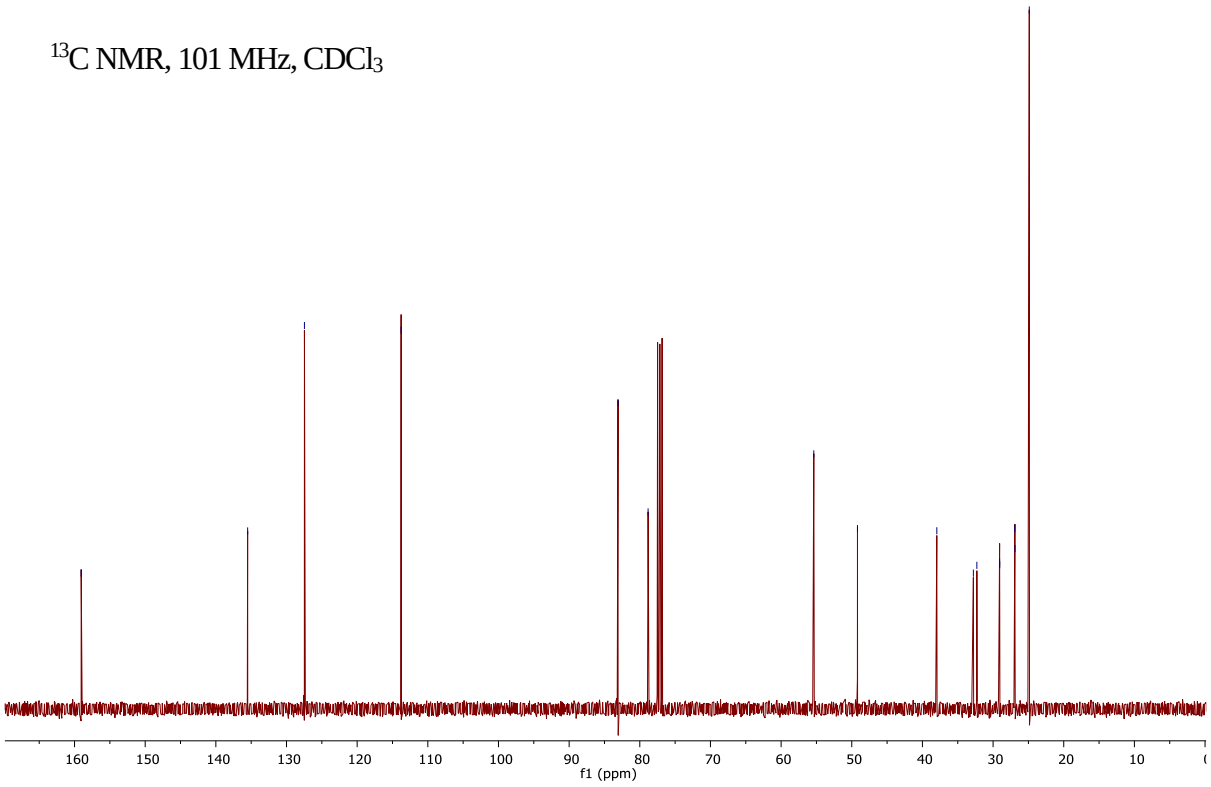
^{13}C NMR, 101 MHz, $CDCl_3$



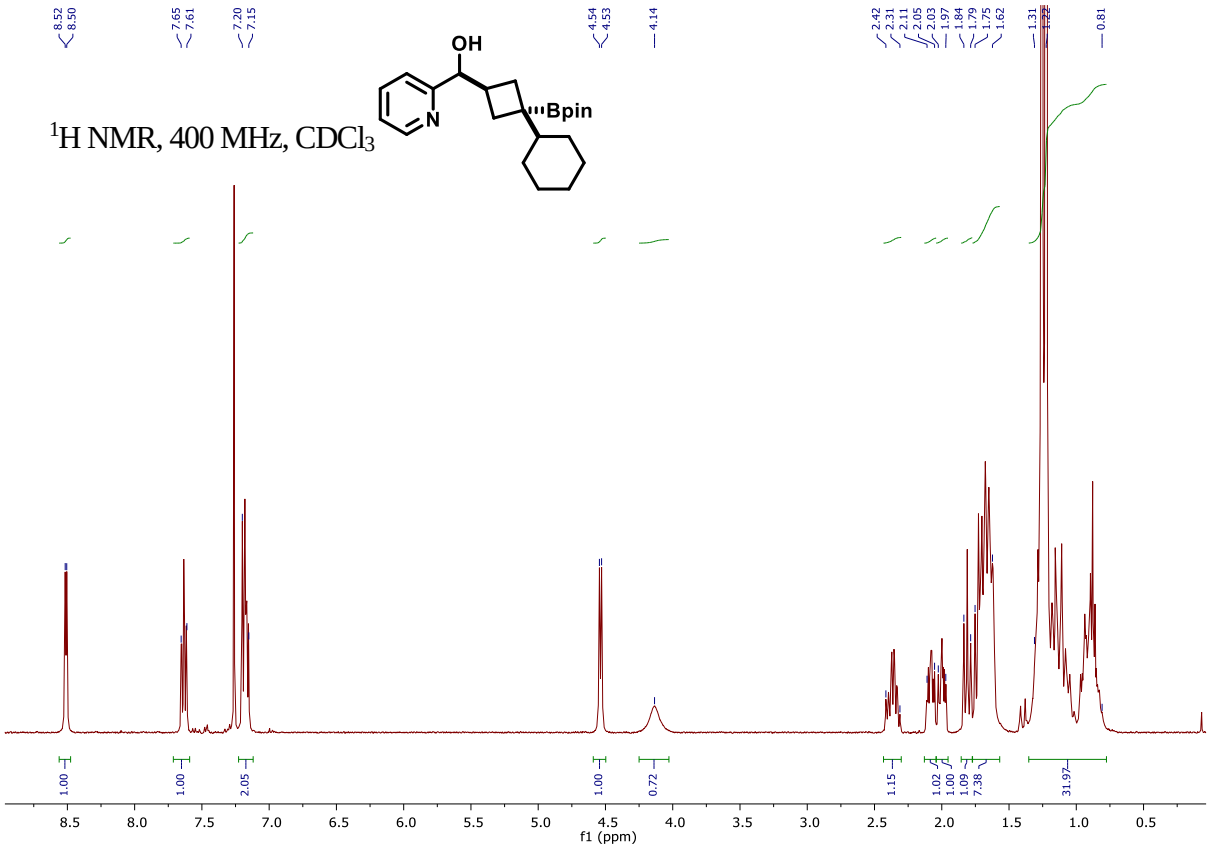
^{1}H NMR, 400 MHz, $CDCl_3$



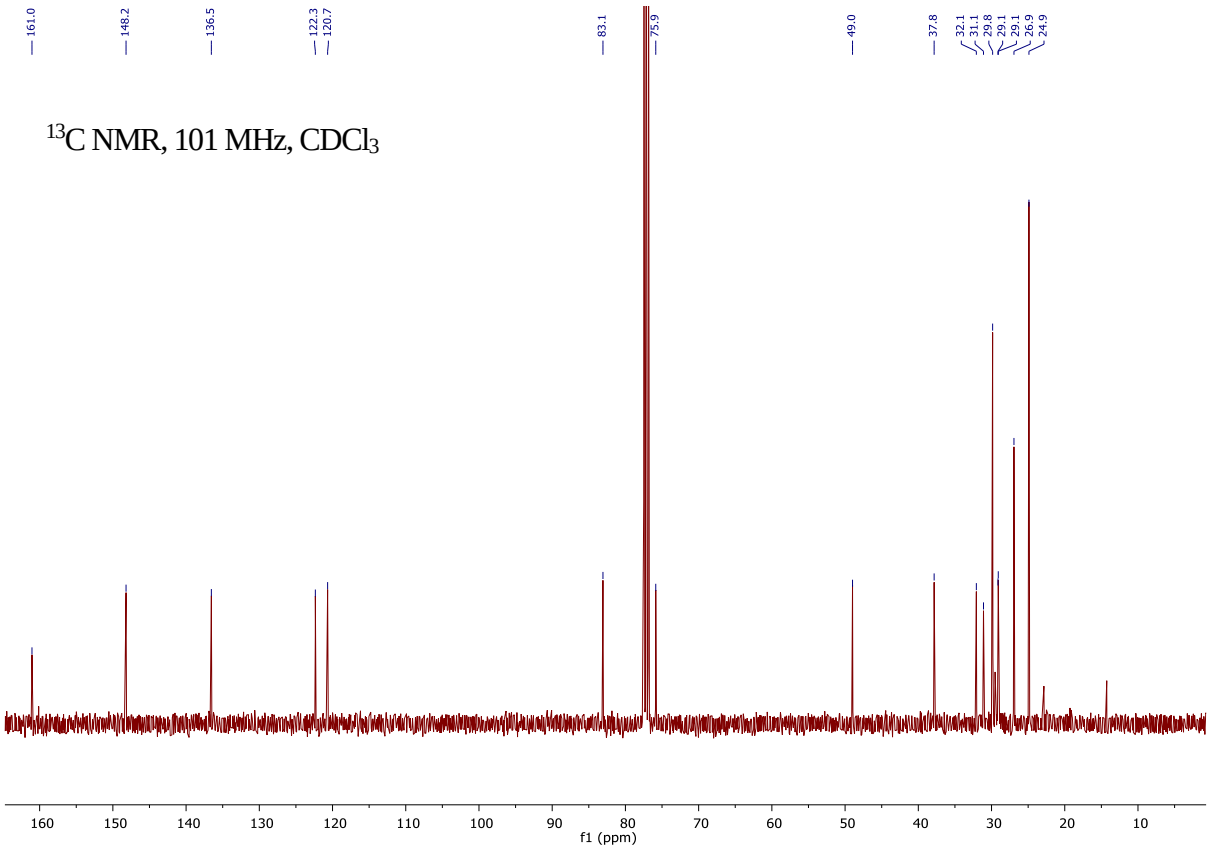
^{13}C NMR, 101 MHz, $CDCl_3$



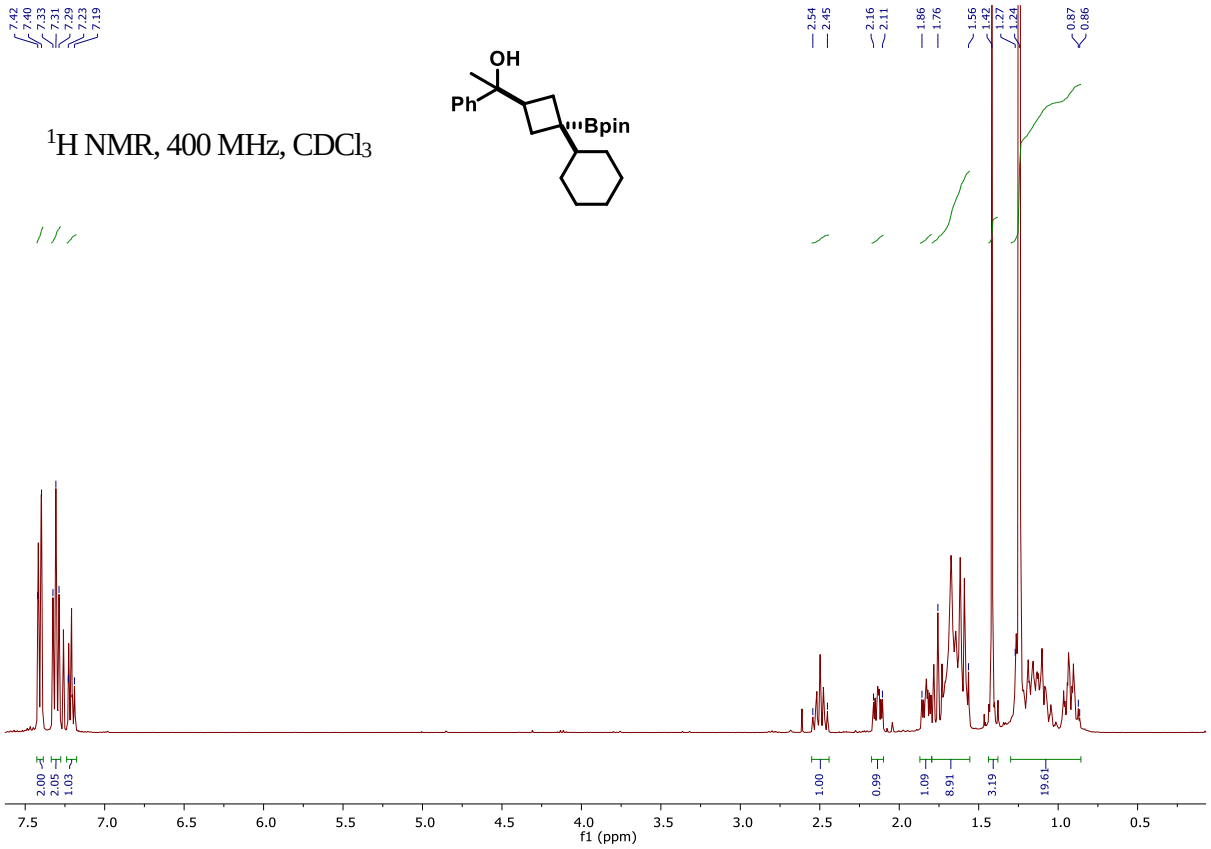
^{1}H NMR, 400 MHz, $CDCl_3$



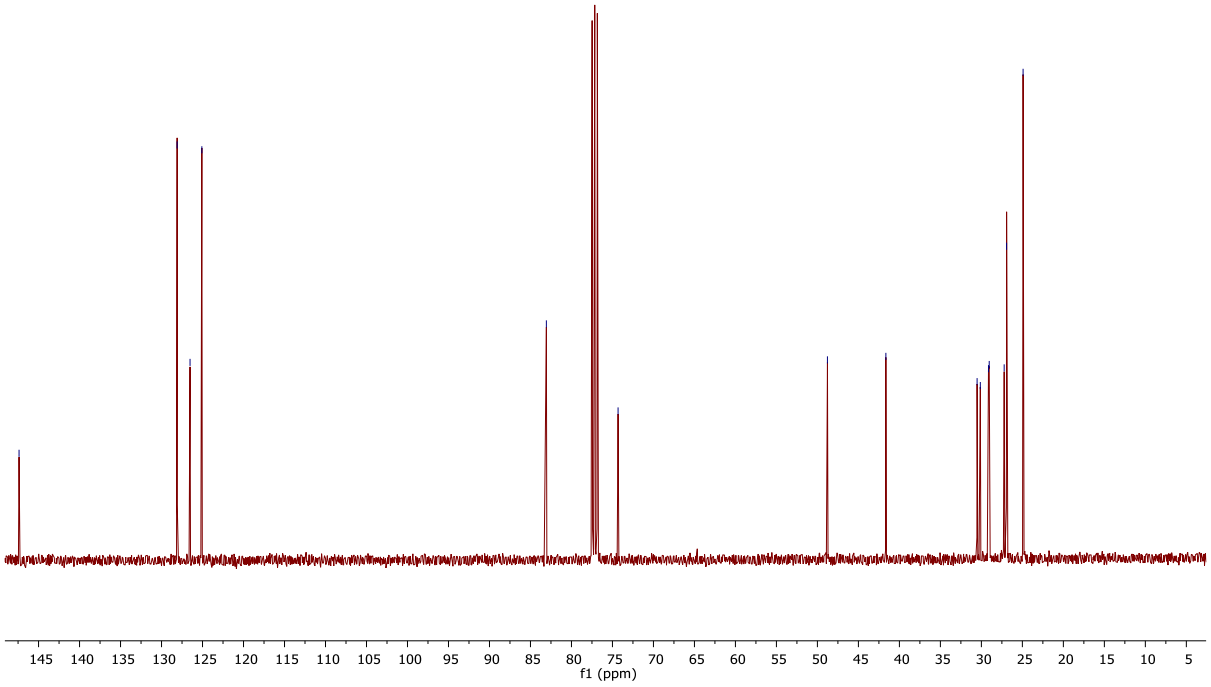
^{13}C NMR, 101 MHz, $CDCl_3$

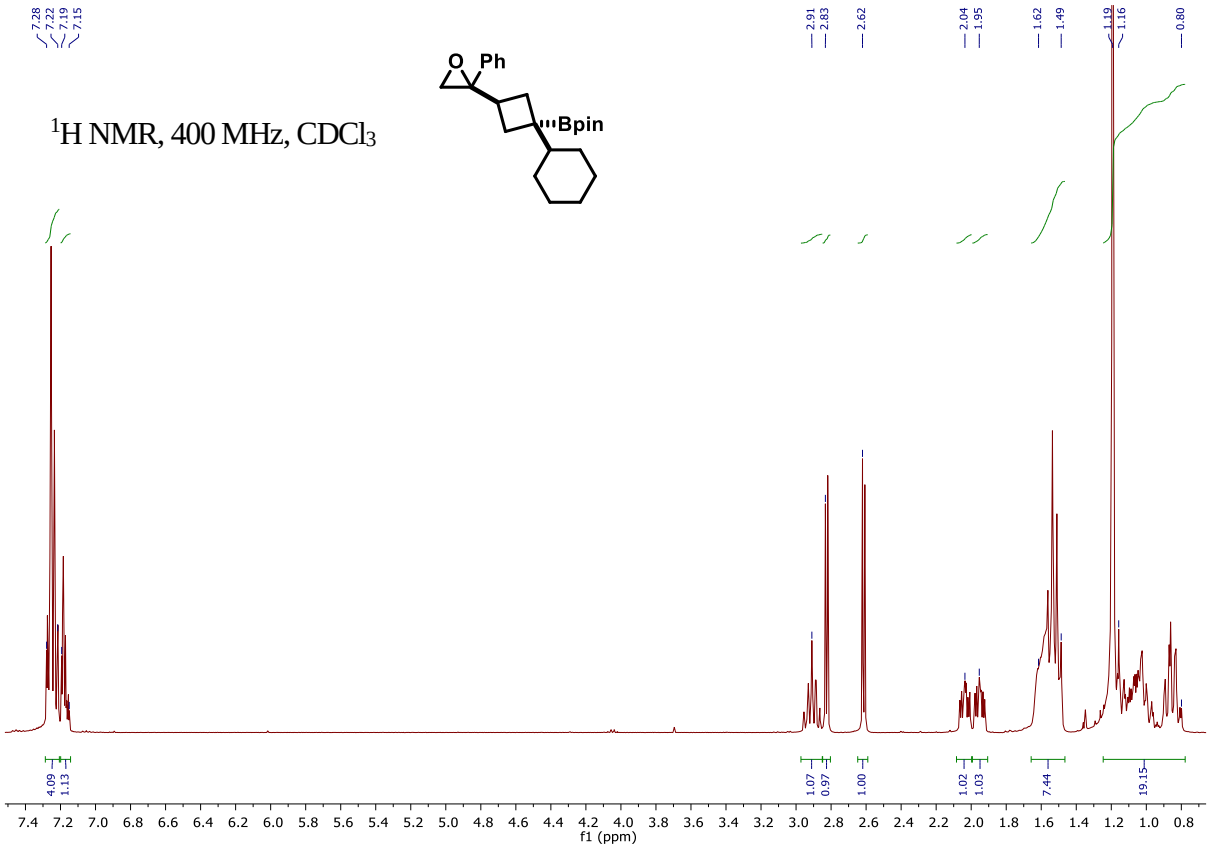


^{1}H NMR, 400 MHz, $CDCl_3$



^{13}C NMR, 101 MHz, $CDCl_3$

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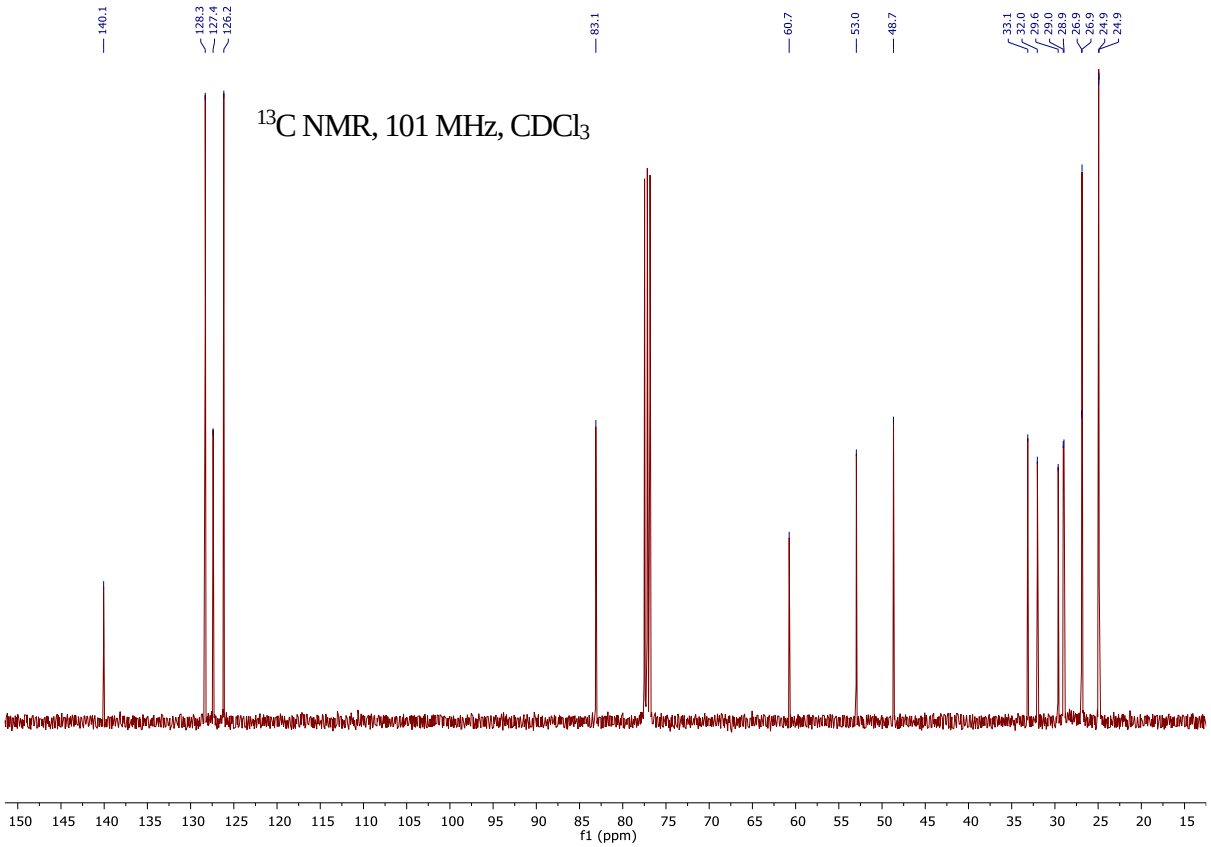
7.22
7.19
7.15
2.91
2.83
2.62
2.04
1.95
1.62
1.49
1.19
1.16
0.80
O
Ph
Bpin
1H NMR, 400 MHz, CDCl3
4.09
1.13
1.07
0.97
1.00
1.02
1.03
7.44
19.15
f1 (ppm)


140.1
128.3
127.4
126.2
83.1
60.7
53.0
48.7
33.1
32.0
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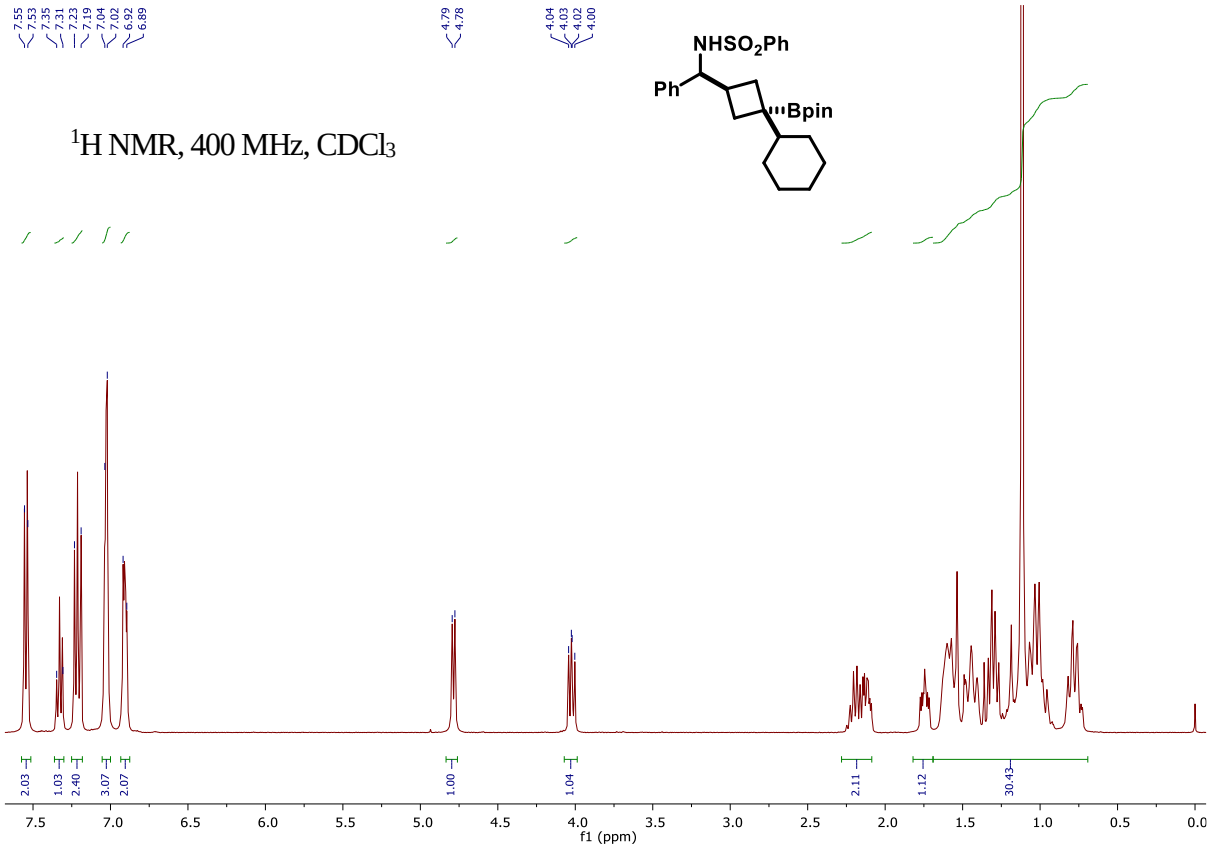
29.0
28.9
26.9
26.9
24.9
24.9
13C NMR, 101 MHz, CDCl3
f1 (ppm)


7.55
7.53
7.35
7.31
7.23
7.19
7.04
7.02
6.92
6.89
4.79
4.78
4.04
4.03
4.02
4.00
NHSO2Ph
Ph
Bpin
1H NMR, 400 MHz, CDCl3
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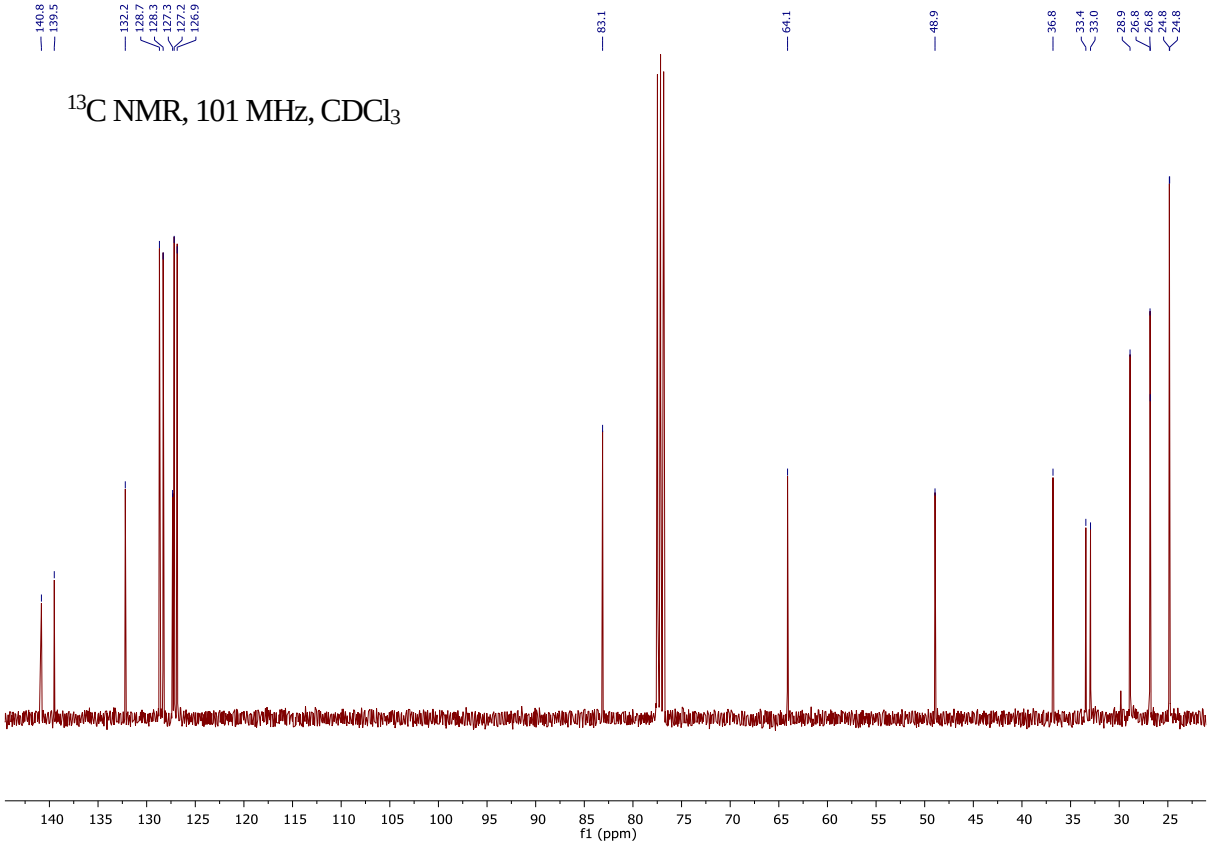
1.03
2.40
3.07
2.07
1.00
1.04
2.11
1.12
30.43
f1 (ppm)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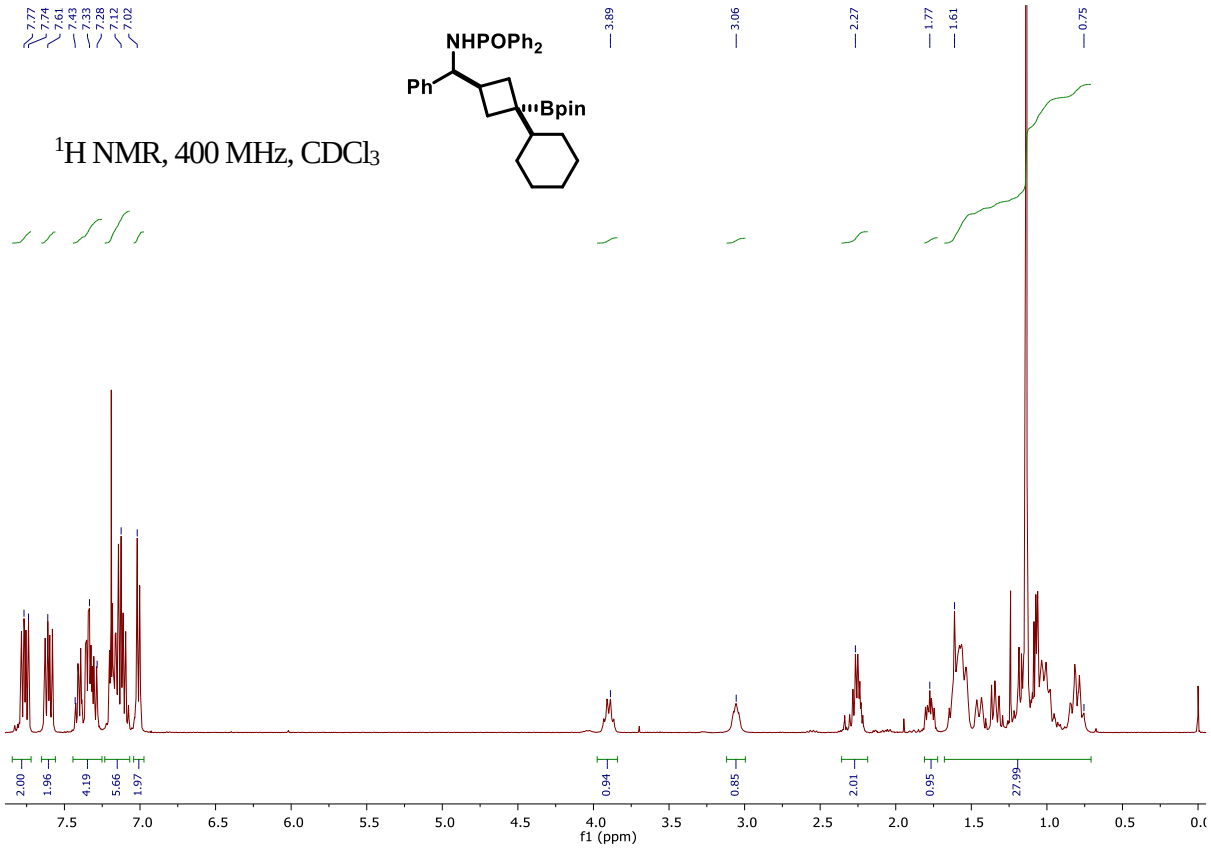
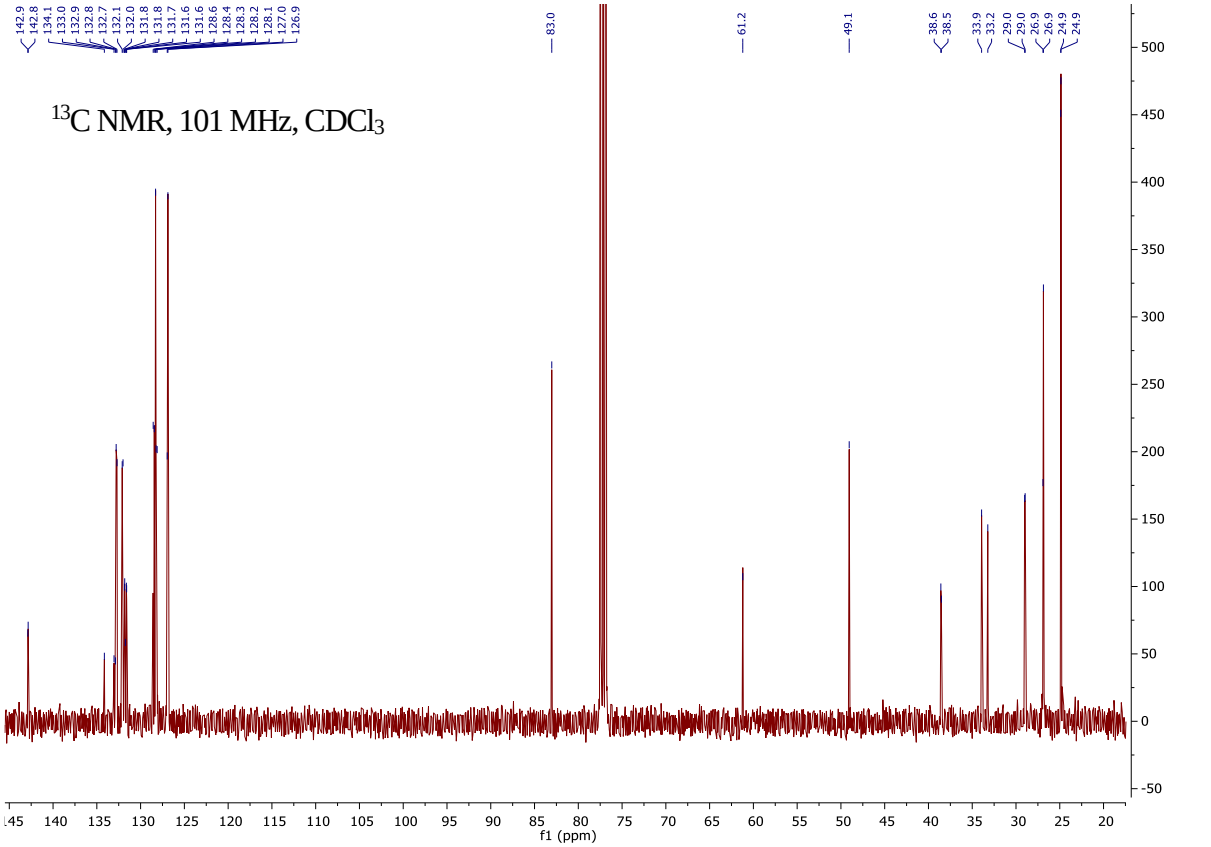
139.5
132.2
128.7
128.3
127.3
127.2
126.9
83.1
64.1
48.9
36.8
33.4
33.0
28.9
26.8
26.8
24.8
24.8
13C NMR, 101 MHz, CDCl3
f1 (ppm)


7.77
7.74
7.61
7.43
7.33
7.28
7.12
7.02
3.89
3.06
2.27
1.77
1.61
0.75
NHPOPh2
Ph
Bpin
1H NMR, 400 MHz, CDCl3
2.00
1.96
4.19
5.66
1.97
0.94
0.85
2.01
0.95
27.99
f1 (ppm)


142.9
142.8
134.1
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132.1
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131.8
131.8
131.7
131.6
131.6
128.6
128.4
128.3
128.2
128.1
127.0
126.9
83.0
61.2
49.1
38.6
38.5
33.9
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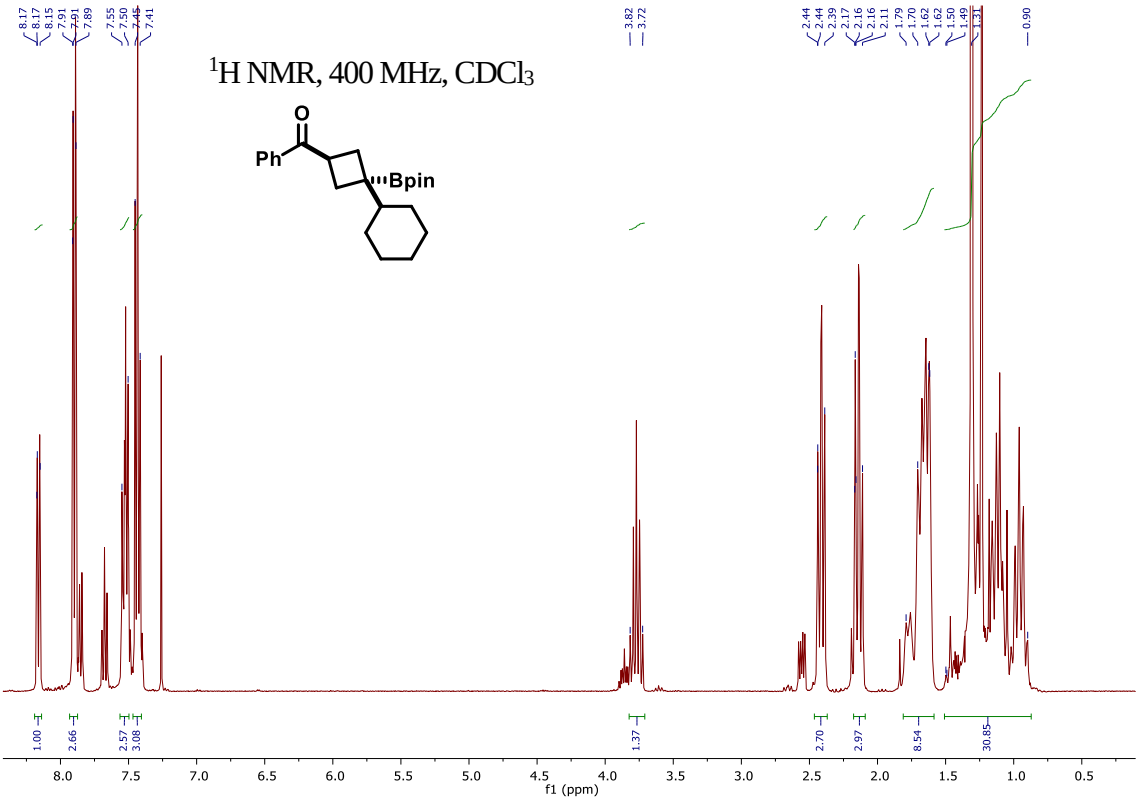
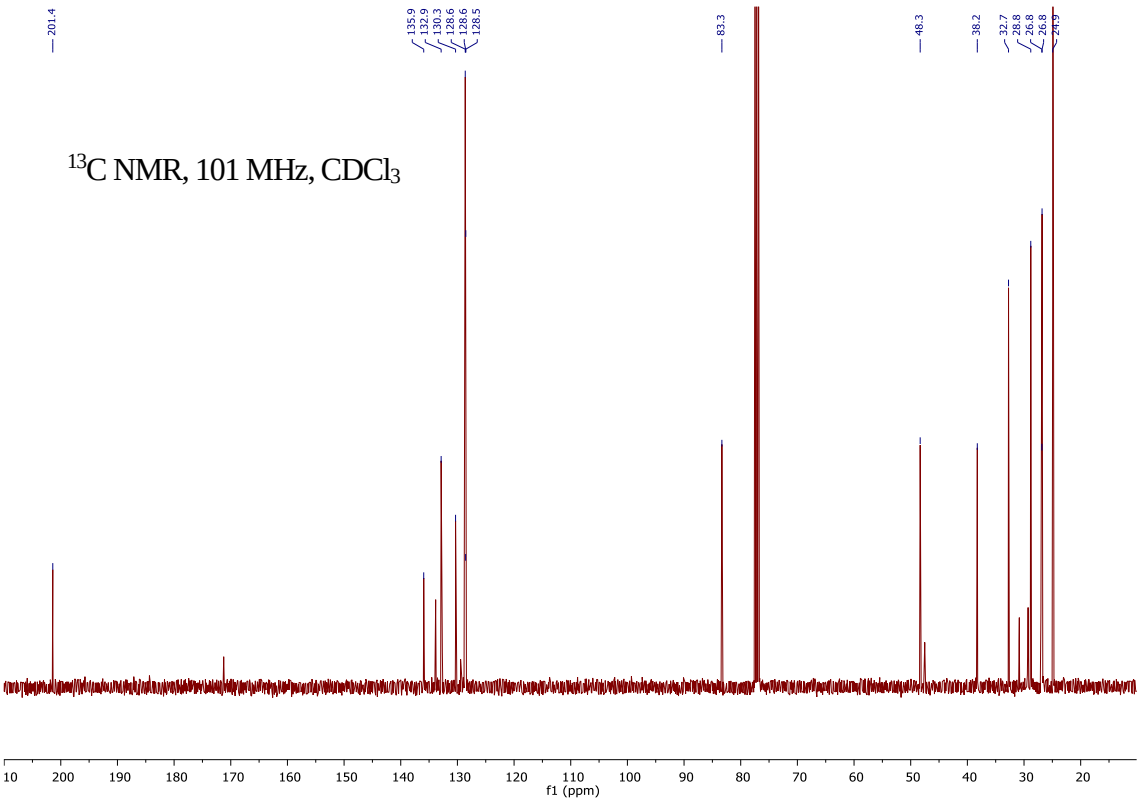
29.0
29.0
26.9
26.9
24.9
24.9
13C NMR, 101 MHz, CDCl3
f1 (ppm)

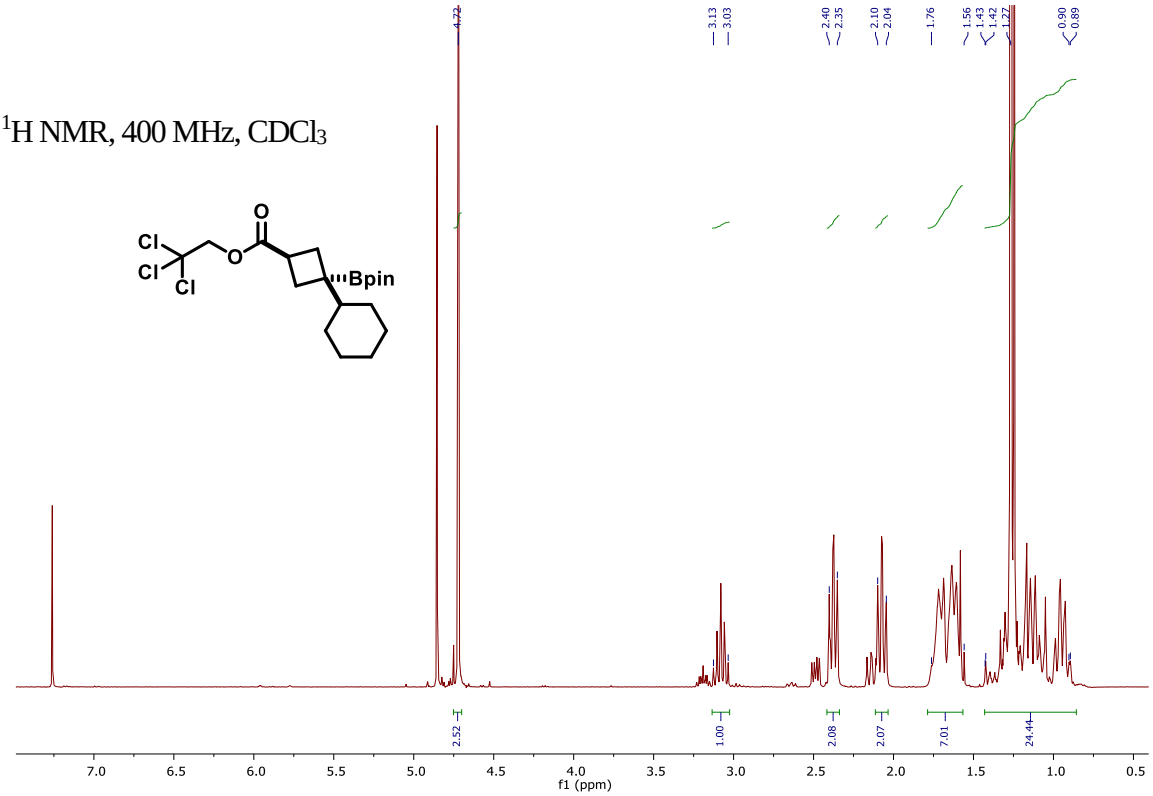


^{1}H NMR, 400 MHz, $CDCl_3$

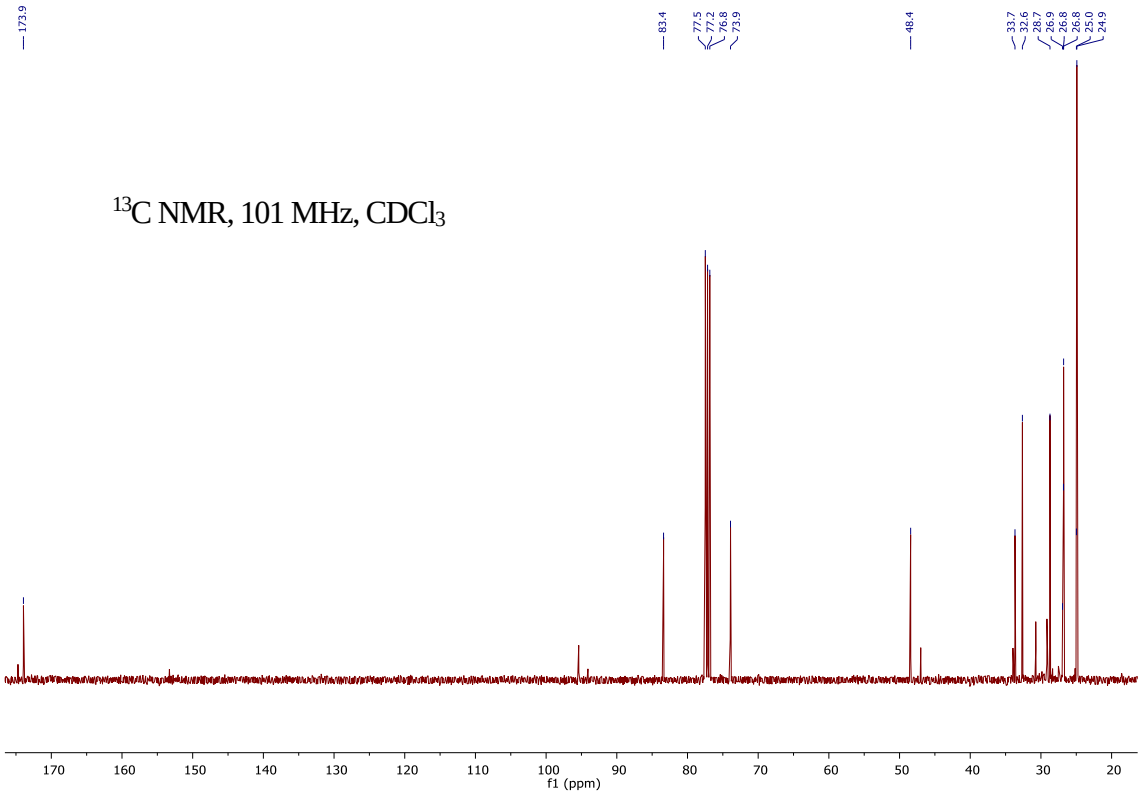


^{13}C NMR, 101 MHz, $CDCl_3$

^{1}H NMR, 400 MHz, $CDCl_3$



^{13}C NMR, 101 MHz, $CDCl_3$



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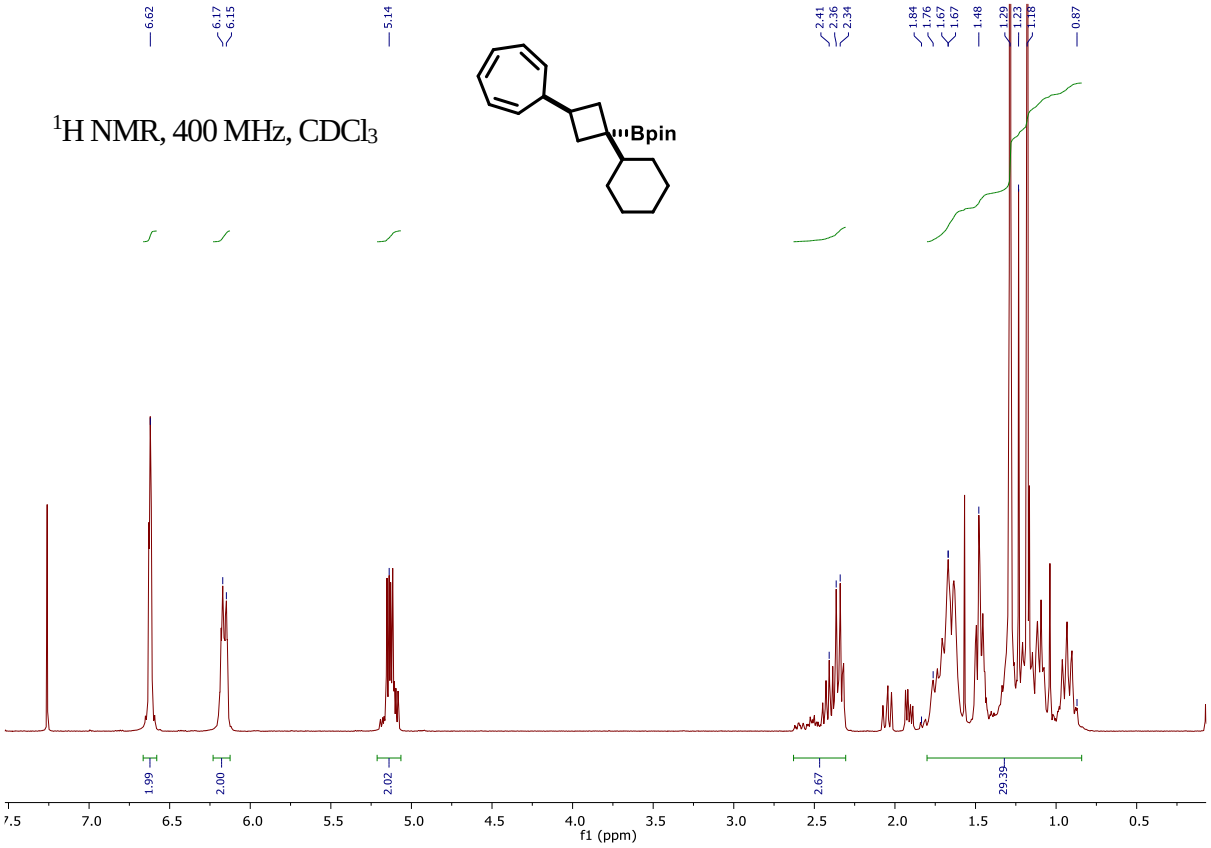

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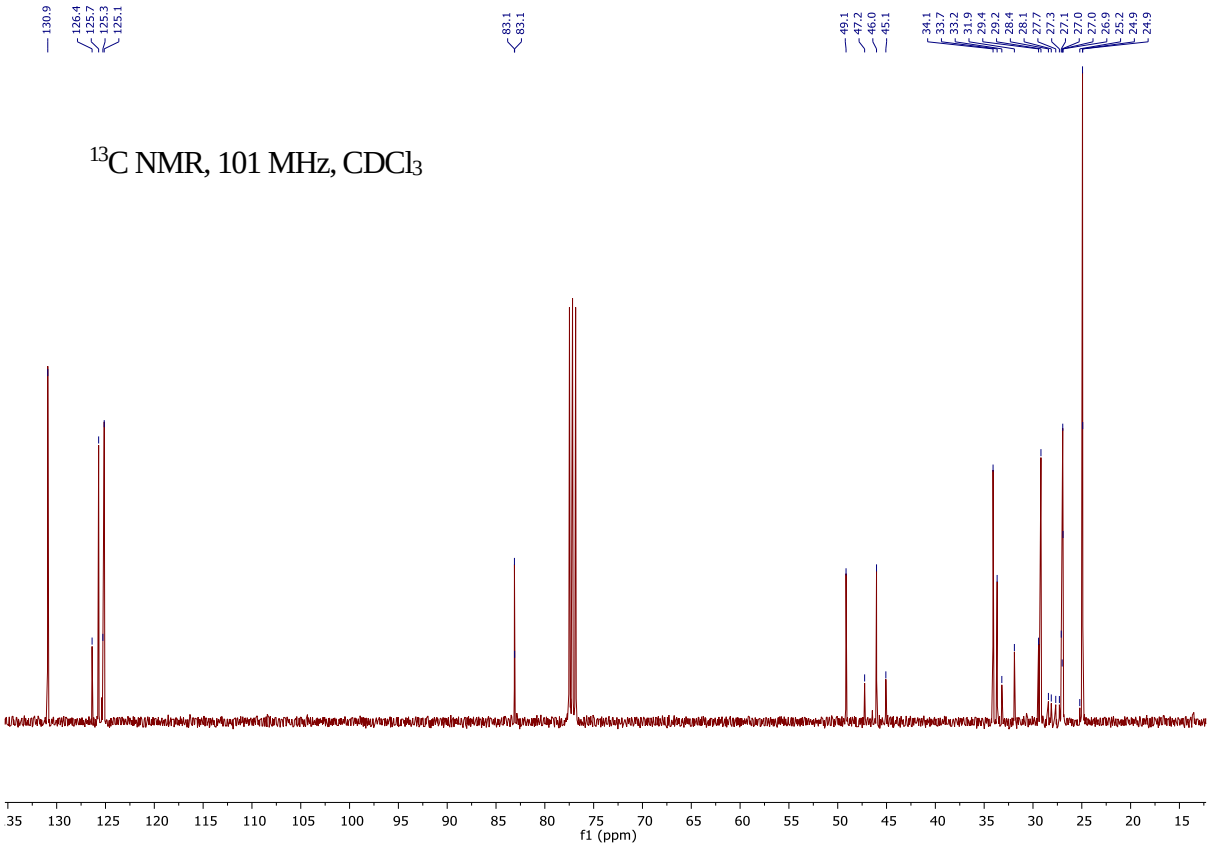
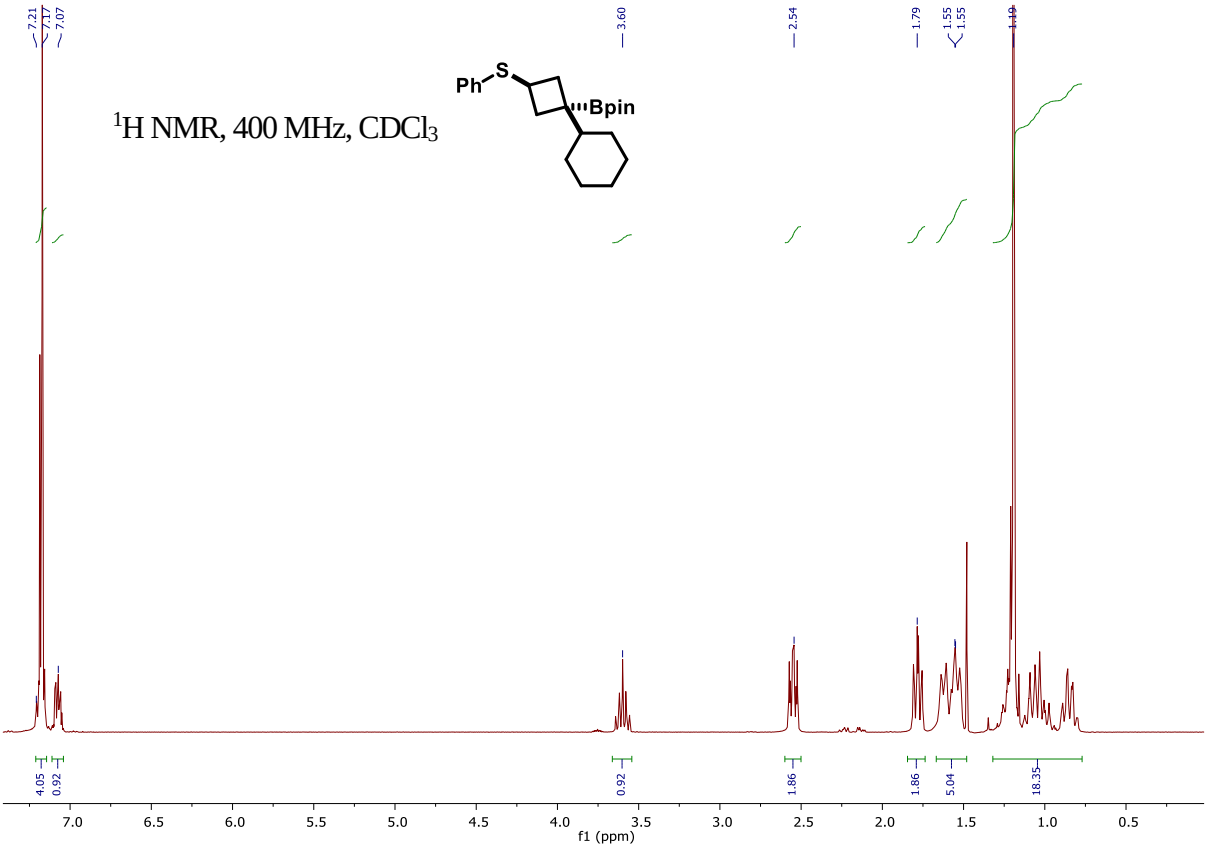
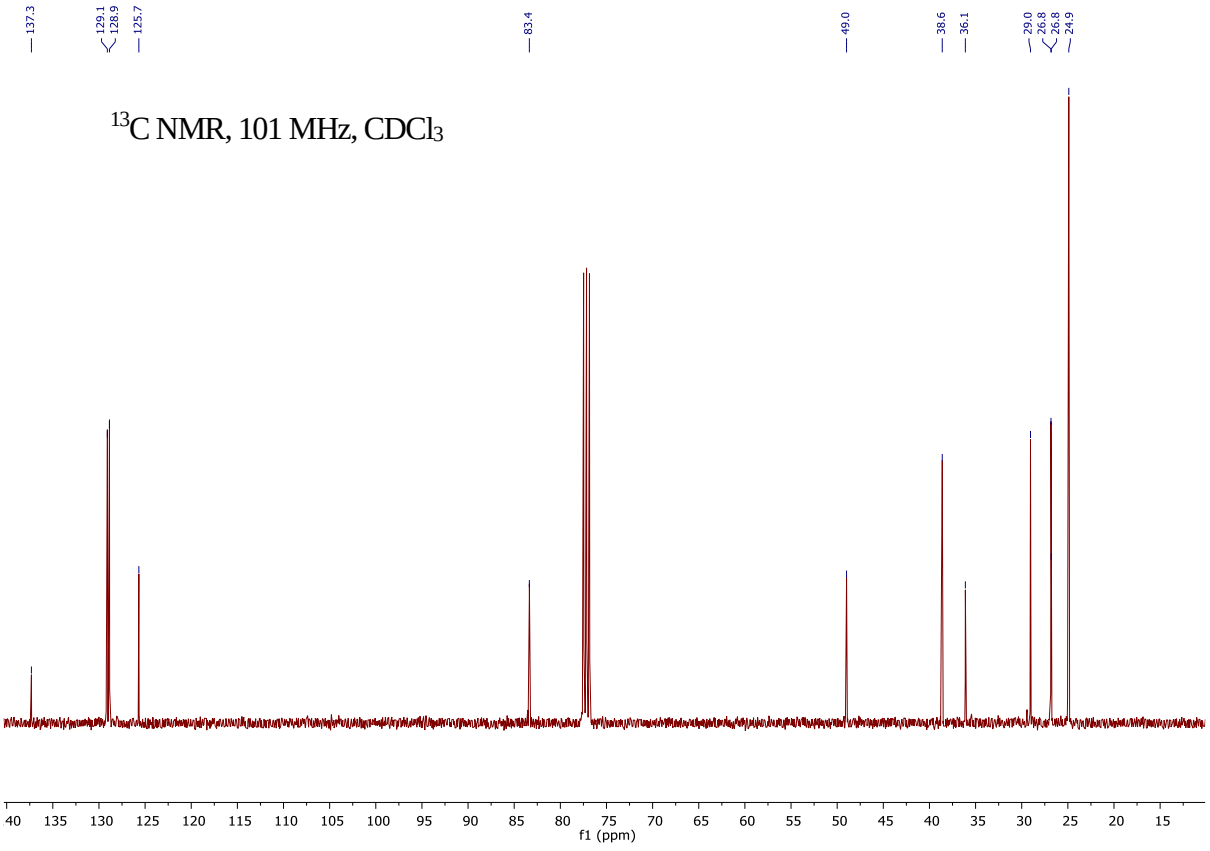




^{1}H NMR, 400 MHz, $CDCl_3$



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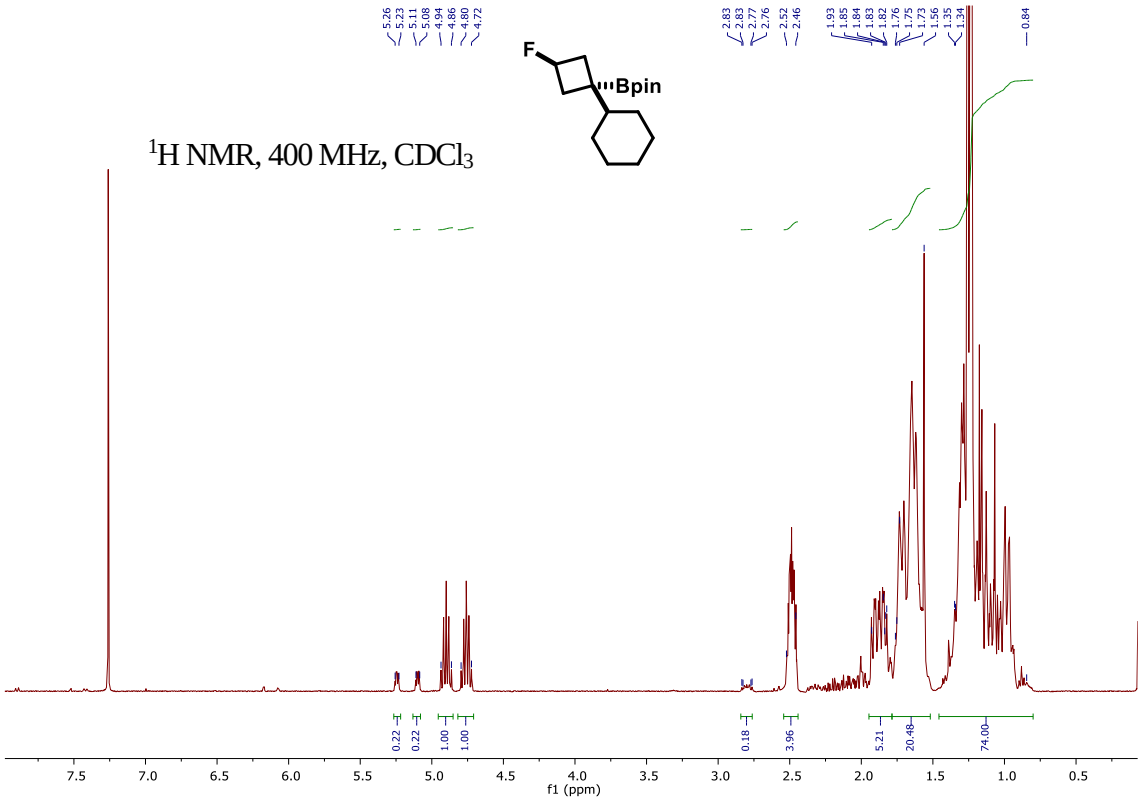

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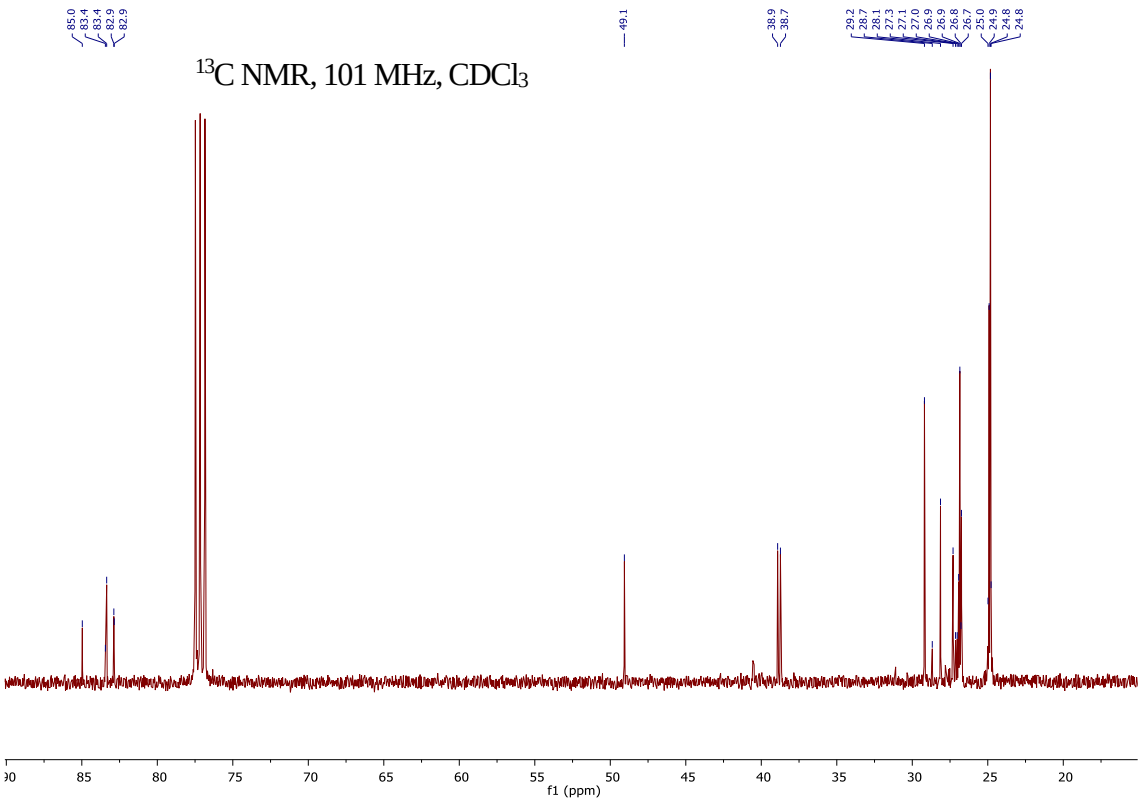

^{13}C NMR, 101 MHz, $CDCl_3$

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